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# Is there a role for vindesine in the treatment of non-small cell lung cancer?

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**Summary**

Vindesine is a semisynthetic derivative of vinblastine which has been evaluated in clinical studies since the late 1970's. The literature on vindesine in the treatment of non-small cell lung cancer has been reviewed and all aspects of vindesine treatment in this disease has been covered. It is concluded that vindesine as a single agent yields a response rate of 18% based on the treatment of 295 patients included in phase II trials (95% confidence limits 13%–22%). No difference was observed among the three major histologic types of non-small cell lung cancer. In phase III trials, the response rate and confidence limits are at a similar level. Combination chemotherapy including vindesine plus cisplatin ranks among the most active treatments in non-small cell lung cancer and is as active as etoposide plus cisplatin, both with respect to response rate and survival. It has not been documented that the addition of one or two other drugs to the combination of vindesine yields an increase in survival. When best supportive care was compared with a combination of vindesine plus cisplatin, the group with chemotherapy was attributed a survival advantage in all three studies published, and the difference was statistically significant in two of these three studies. Thus, vindesine has a well documented activity in non-small cell lung cancer and ranks among the most active single agents in this disease. Vindesine is also part of several active combination chemotherapies among which the combination of vindesine plus cisplatin is particularly interesting, because it has been repeatedly shown to prolong survival as compared to supportive care. Especially this latter point leads to the conclusion that there is a role for vindesine in the treatment of non-small cell lung cancer. However, the concept of chemotherapy in this disease remains investigational even though the advances seen in recent years clearly merit further studies.

## Introduction

In spite of the fact that clinicians have used cytostatic agents in the treatment of non-small cell lung cancer (epidermoid, adeno- and large cell carcinoma; WHO I, III, IV) since the late 1950's, it is still uncertain which of the many agents of combinations of cytostatic drugs are the most efficacious and therefore should be accepted or recommended for general use.

The predicament is both a reflection of the lack of highly effective systemic treatments for NSCLC and a result of the methodological dilemmas which still exist in the design, execution, analysis and conclusions from the clinical trials performed during the last 3 decades.

We have reviewed the existing literature going back to the 1970's and focusing on the usefulness of vindesine in the treatment of non-small cell lung cancer, both as a single agent, combination chemotherapy, and when used in combined modality therapies covering both phase II and III trials.

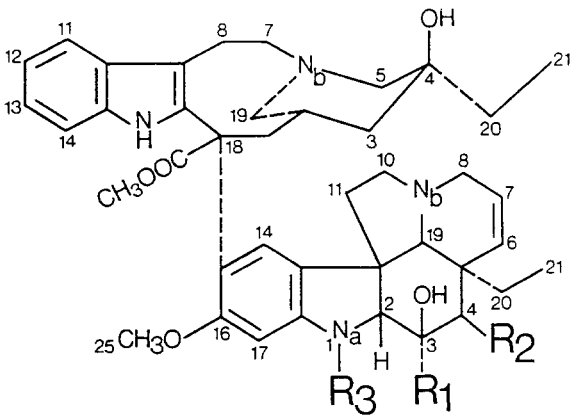
Each phase of clinical drug development presents each own set of dilemmas. Although the purpose of phase II and III trials in clinical oncology is conceptually straight forward, a number of theoretical and practical problems make it a very treacherous stage in clinical drug testing. The problems relate both to patient selection, response assessment, treatment intensity and reporting procedures [1].

In randomized studies the endpoints evaluated comprise both survival and response. While the survival calculation in itself is rather straight forward, the evaluation of response and the clinical impact of response represent several pitfalls [2]. First of all, the distribution of patients with bidimensionally measurable disease and unidimensionally measurable (evaluable) disease in a study may influence the response rate observed. In a multiple, logistic regression analysis among patients with inoperable adenocarcinoma of the lung treated with a randomized chemotherapy trial, Sørensen *et al.* [2] reported that among 27 pretreatment variables, the only significant predictor of response was bidimensionally measurable disease ($p = 0.002$). Also, Ruckdeschel *et al.* [3] observed a somewhat higher overall response rate for patients with NSCLC having measurable disease as compared to non-measurable disease in a multiple regression analysis ($p = 0.04$). This observation, however, was not confirmed in a later study by the same group of investigators [3]. Eagan *et al.* [4] observed no differences in response rate between patients with measurable or evaluable disease in a univariate analysis.

It is conceivable that the low response rate of patients with evaluable disease observed in the two studies cited above may not be caused by biological differences. Rather, it reflects the difficulties of quantitating response, as previously emphasized by Warr *et al.* [5], especially when the lesions are not bidimensionally measurable. Obviously, response assessment is more difficult in partial remission than in complete remission and, unfortunately, the majority of responses in clinical trials in NSCLC are only partial.

## Impact of chemotherapy on quality of life in non-small cell lung cancer patients

Trials with chemotherapy in NSCLC have yielded varying results, but complete remissions are rare. Responses have usually been observed in less than 50% of the patients and in most studies enhanced survival has not been observed. Furthermore, there has been some concern regarding toxicity. Hence, lack of significant efficacy of chemotherapy together with troublesome side effects has prompted a somewhat nihilistic view on the use of chemotherapy in NSCLC. Some studies to be discussed in relation with Table 10 have demonstrated a significant, albeit modest, impact of chemotherapy on survival as compared to supportive care only [6,7].



| | $R_{1(3)}$ | $R_{2(4)}$ | $R_3$ |
|---|---|---|---|
| VINDESINE | $CONH_2$ | OH | $CH_3$ |
| VINCRISTINE | $COOCH_3$ | $OCOCH_3$ | CHO |
| VINBLASTINE | $COOCH_3$ | $OCOCH_3$ | $CH_3$ |

*Fig. 1.* Structural formulas of vindesine, vincristine, and vinblastine

Little emphasis has been placed on the impact chemotherapy may have on the quality of life among responding and non-responding patients. This issue is of importance for determining the overall role of chemotherapy in this disease. Measuring quality of life in patients with NSCLC is difficult, as previously emphasized [8–10]. Though troublesome, some results can be extracted from the literature on this topic.

Firstly, Osoba *et al.* [11] reported a 44% response rate in advanced NSCLC after chemotherapy with VP-16, cisplatin and bleomycin and showed that the objective responses correlated closely with the improvement of symptoms. In 51% of the patients included, all symptoms were temporarily controlled. Also a study from Memorial Sloan-Kettering Cancer Center evaluated whether an objec-

tive tumour response with chemotherapy resulted in subjective benefit to patients with stage III NSCLC [12]. Twenty-nine patients who achieved a major response to chemotherapy were prospectively evaluated for presence and severity of symptoms using a series of 100 mm visual analogue scales prior to beginning chemotherapy with vindesine and cisplatin with or without mitomycin. Eighteen patients could be reevaluated day 70 after initiation of treatment. The symptoms evaluated were pain, cough, hemoptysis, dyspnea, and anorexia. In addition, Karnofsky performance status was measured. Out of 8 patients with initial pain, 6 patients had discontinued all pain medication, and the other two had decreased pain medication. Among 10 patients who presented with significant cough, 8 reported improvement, one worsening, and out of the 12 patients who presented with dyspnea, 10 had no change or improvement, while 15 of 18 patients either maintained or improved their appetite. Karnofsky performance status was either improved or maintained in 16 of 18 patients. Thus, the majority of patients with NSCLC who achieved a major response to chemotherapy simultaneously experience improvement of symptoms and improvement or maintenance of performance status.

Similar results were reported in a Spanish study by Fernandez *et al.* [13]. The study included 31 patients with stage III to IV NSCLC who were treated with vindesine plus cisplatin in combination with either mitomycin-C or ifosfamide. The effect on symptom status was assessed with both categorical scales and 100 mm visual analogue scales used by the patients themselves to report on several symptoms. After chemotherapy, 17 of 19 patients (89%) gained weight; 20 presented anorexia, 10 of those (50%) improved, 15 patients had pain, and 7 of those (47%) were alleviated. Cough was reported in 22 patients and was ameliorated in 10 (45%). Hemoptysis disappeared in 10 of 11 patients (91%), and out of 9 patients who had dyspnea, 7 improved (78%); astenia was attenuated in 8 of 16 patients (50%). When compared with Karnofsky performance status, no difference was found before or after chemotherapy and response rate in the study was 58%. All responses in the study were partial. There were no differences in frequency of patients with improvement of symptoms among patients with objective response and patients without.

Based on these results, it is probable that, apart from the objective responses achieved, a large proportion of patients benefit from chemotherapy as demonstrated by marked relief of symptoms. It should be noted, however, that this has not been a universal finding, as a study by Bakker *et al.* [14] reported that performance status and body weight among 28 patients with NSCLC who received vindesine, cisplatin and bleomycin dropped significantly during chemotherapy, both among responders and non-responders. Performance status after discontinuation of chemotherapy approached pretreatment scores in responders only.

## Vindesine

The vinca alkaloids, vincristine and vinblastine, are two members of a large family of alkaloids derived from the Madagascan Periwinkle (Catharanthus roseus) previously known as Vinka rosea L, a member of the family Apocynacea. Vindesine is a semisynthetic modification of this group with the structure shown in Fig. 1. Vindesine, or deacetyl vinblastine amide sulfate (DVAS), is thus a semisynthetic derivative of vinblastine from which it differs by one hydroxyl carboxyamino group on its side chain. This minor distinction, however, is responsible for profound differences in the oncolytic spectrum, potency, and toxicity of the two compounds.

Vinblastine and vincristine were introduced into the clinic in the early 1960's, while vindesine entered phase I studies in 1977 [15,16]. The principal intracellular target of vindesine is tubulin. In the actively dividing cell, tubulin units are assembled into microtubules which are disassembled into units during or following their functional activity. The vinca alkaloids, which bind to the tubulin units, prevent the ordered assembly into a microtubule and, instead, at low concentrations lead to the formation of pseudo-crystalline structures which do not appear to have any functional activity.

Microtubular elements are involved in many critically important activities of living cells and, in par-

*Table 1.* Vindesine as single agent in phase II trials, epidermoid lung cancer (WHO I)

| Schedule mg/m² i.v. | No. of patients | | | No. of responders | | | Response rate (95% CL) | Median duration (months) | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | NT | PT | Total | CR | PR | Total | | | |
| Weekly 3–4 | – | – | 14 | – | 3 | 3 | 14 (5–51) | – | 19 |
| Weekly 3 | 21 | 0 | 21 | 0 | 0 | 0 | – (0–16) | – | 20 |
| Weekly 4 | 14 | 5 | 19 | 0 | 2 | 2 | 11 (1–33) | 3 | 21 |
| Weekly 3–4 | 18 | 17 | 35 | 0 | 9 | 9 | 26 (57–88) | 2 | 22 |
| Weekly 3–4 | – | – | 15 | 1 | 4 | 5 | 33 (12–62) | 3 (1–6.5) | 23 |
| Weekly 3 | – | – | 7 | – | 1 | 1 | 15 (0–58) | 3 | 24 |
| Weekly 3 | 24 | 0 | 24 | – | 2 | 2 | 8 (1–27) | – | 25 |
| Total | | | 135 | 1 | 21 | 22 | 16 (10–24) | – | |

Abbreviations: NT, no prior treatment; PT, prior treatment; CR, complete response; PR, partial response; CL, confidence limits.

*Table 2.* Vindesine as single agent in phase II trials. Adenocarcinoma of the lung (WHO III)

| Schedule mg/m² i.v. | No. of patients | | | No. of responders | | | Response rate (95% CL) | Median duration (months) | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | NT | PT | Total | CR | PR | Total | | | |
| Weekly 3–4 | – | – | 29 | – | – | 6 | 21 (8–40) | – | 19 |
| Weekly 3 | 7 | 0 | 7 | | | 1 | 14 (0–58) | – | 20 |
| Weekly 3 | 0 | 7 | 7 | – | – | 0 | 0 (0–41) | – | 24 |
| Weekly 4 | 21 | 1 | 22 | 1 | 5 | 6 | 27 (11–50) | 6 (2–15+) | 21 |
| Weekly 3–4 | 5 | 5 | 10 | – | 2 | 2 | 20 (3–56) | 2 | 22 |
| Weekly 3–4 | – | – | 8 | – | 3 | 3 | 38 (9–76) | 3 | 23 |
| Weekly 4 | 17 | 0 | 17 | – | 5 | 5 | 29 (10–56) | | 25 |
| Weekly 3 | 17 | 0 | 17 | – | 1 | 1 | 6 (0–29) | 2 | 26 |
| Weekly 3 | – | – | 15 | – | 2 | 2 | 15 (2–40) | 5 | 27 |
| Total | | | 132 | 1 | 25 | 26 | 20 (14–28) | | |

Abbreviations: see Table 1

ticular, tumour invasiveness may be dependent on the activities of microtubular processes. Neurotoxic side effects may also be related to the effects of vindesine on these organelles. Changes in nerve conduction velocities, axonal degeneration and demyelination and inhibition of rapid axonal transport have been recorded following vinca alkaloid treatment [17]. The terminal half-life of vindesine is 24 hours and its plasma clearance is intermediate between those of vinblastine and vincristine. The maximal tolerated dose is 4 mg/m² per week. The *acute* dose-limiting toxicity is myelosuppression (nadir was reached by days 7–8 and recovery by days 11–13) [18], while neurotoxicity is the limiting factor in more prolonged treatment. The accumulated neurotoxicity consists of parethesias, without motor impairment, and hematologic toxicity, with leucopenia, and sometimes alopecia, astenia and muscle pains [18].

## Single agent therapy

The phase II trials evaluating the activity of vindesine in non-small cell lung cancer when used as a single agent are depicted for the three major histologic types in Tables 1–3 (epidermoid, Table 1 ; adenocarcinoma, Table 2; large cell carcinoma, Table 3) [19–27]. Overall, 295 patients have been included in the study with 135, 132 and 28 patients

*Table 3.* Vindesine as single agent in phase II trials. Large cell carcinoma (WHO IV)

| Schedule mg/m² i.v. | No. of patients | | | No. of responders | | | Response rate (95% CL) | Median duration (months) | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | NT | PT | Total | CR | PR | Total | | | |
| Weekly 3–4 | – | – | 3 | – | 1 | 1 | (1–91) | – | 19 |
| Weekly 3 | 9 | 0 | 9 | – | 3 | 3 | (7–70) | – | 20 |
| Weekly 4 | 11 | 2 | 13 | – | 1 | 1 | 8 (0–36) | 3 | 21 |
| Weekly 4 | – | – | 3 | – | – | – | – (0–71) | – | 23 |
| Total | – | – | 28 | 0 | 5 | 5 | 18 (6–37) | | |

Abbreviations: see Table 1

*Table 4.* Summary of studies evaluating vindesine as single agent in non-small cell lung cancer (3–4 mg/m² i.v. weekly)

| Histologic type | No. of patients | Responders | | | Response rate (95% CL) |
|---|---|---|---|---|---|
| | | CR | PR | Total | |
| Epidermoid (WHO I) | 135 | 1 | 21 | 22 | 16 (10–24) |
| Adenocarcinoma (WHO III) | 132 | 1 | 25 | 26 | 20 (14–28) |
| Large cell carcinoma (WHO IV) | 28 | 0 | 5 | 5 | 18 (6–37) |
| Total | 295 | 2 | 51 | 53 | 18 (13–22) |

Abbreviations: see Table 1

having epidermoid, adeno- or large cell carcinoma. Twenty-two, 26 and 5 patients responded, yielding a response rate of 16%, 20% and 18%, respectively, thus giving no indication for difference in sensitivity of vindesine among the various histologic types (Table 4).

### *Vindesine versus combination chemotherapy – randomized trials*

In Table 5 the trials using vindesine as a single agent are depicted. They consist of 6 trials with a comparison of vindesine versus combination chemotherapy, while the seventh trial compares vindesine versus vincristine.

A trial by Sørensen *et al.* [28] on behalf of the Copenhagen group included exclusively patients with previously untreated non-resectable adenocarcinoma. A total of 279 patients entered a prospective, randomized trial comparing vindesine to a combination of lomustine (CCNU), cyclophosphamide (CTX), methotrexate (MTX) in a regimen including all 4 drugs. Response assessment was possible for 218 patients, while 259 were evaluable for survival. Response rate was similar, 22%, 23% and 27%, respectively, as was median duration of response (15 weeks, overall) and survival (29 weeks, overall). Noteworthy was the observation that patients with dose limiting toxicity had a significantly higher response rate and longer survival than patients without toxicity (28% versus 9%, and 35 versus 15 weeks, respectively). The study thus confirmed the vindesine single agent activity in adenocarcinoma of the lung observed in phase II studies, and it also suggested that the activity was dose-dependent.

Another trial was performed by Luedke and colleagues [29] who randomized untreated patients with advanced non-small cell lung cancer to one of three regimens: vindesine 3 mg/m² every 2 weeks; vindesine 3 mg/m² weekly for 5 weeks followed by a dose every 2 weeks plus mitomycin-C 20 mg/m² day 1 and then 15 mg/m² every 6 weeks; or vindesine at the more intensive dose rate plus cisplatin 120 mg/m² with forced diuresis on days 1, 29 and

*Table 5.* Randomized trials comparing vindesine alone versus other chemotherapy

| Treatment | No. of patients | | | | Histology % | | | Response | | | | 95% Confidence limits (%) | Median duration of response (weeks) | survival | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PC | PI | NT | Total | SQ | AD | LC | CR | PR | Total | (%) | | | | |
| VDS | 0 | 0 | 71 | 71 | 0 | 100 | 0 | 5 | 11 | 16 | (22) | 13–34 | 12 | 29 | 28 |
| CCNU/CTX/MTX | 0 | 0 | 74 | 74 | 0 | 100 | 0 | 2 | 15 | 17 | (23) | 14–34 | 16 | 29 | |
| VDS/CCNU/CTX/MTX | 0 | 0 | 73 | 73 | 0 | 100 | 0 | 2 | 18 | 20 | (27) | 18–39 | 16 | 24 | |
| VDS | 0 | 45 | 83 | 128 | 31 | 44 | 25 | 0 | 1 | 1 | (1) | 0–4 | 12 | 15 | 29 |
| VDS/MMC | 0 | 37 | 85 | 122 | 35 | 46 | 19 | 1 | 32 | 33 | (27) | 19–36 | 12 | 20 | |
| VDS/CDDP | 0 | 30 | 95 | 125 | 34 | 45 | 21 | 2 | 22 | 24 | (19) | 13–28 | 12 | 25 | |
| VDS | 0 | – | – | 42 | 40 | 45 | 15 | 0 | 6 | 6 | (14) | 5–29 | 14 | 18 | 30 |
| VDS/CDDP | 0 | – | – | 41 | 46 | 46 | 8 | 0 | 11 | 11 | (27) | 14–43 | 13 | 26 | |
| VDS/CDDP/MMC | 0 | – | – | 41 | 41 | 49 | 10 | 0 | 8 | 8 | (20) | 9–35 | 27 | 17 | |
| VDS | 0 | 0 | 54 | 54 | 69 | 13 | 18 | 0 | 3 | 3 | (6) | 1–15 | – | 17* | 31 |
| VDS/CDDP | 0 | 0 | 51 | 51 | 70 | 14 | 16 | 0 | 14 | 14 | (27) | 16–42 | – | 46* | |
| VDS | 0 | 4 | 13 | 17 | – | – | – | 0 | 3 | 3 | (18) | 4–43 | – | | 32 |
| VDS/CDDP | 0 | 3 | 11 | 14 | – | – | – | 1 | 3 | 4 | (31) | 8–58 | – | | |
| VDS | – | 0 | 28 | 28 | 100 | – | – | 0 | 7 | 7 | (25) | 10–44 | 7 | 14 | 33 |
| DOX/CTX | – | 0 | 28 | 28 | 100 | – | – | 0 | 1 | 1 | (5) | 6–37 | – | 14 | |
| VDS | 0 | – | – | 35 | – | – | – | 0 | 5 | 5 | (14) | 5–30 | – | 16 | 34 |
| VCR | 0 | – | – | 28 | – | – | – | 0 | 0 | 0 | (0) | 0–12 | – | 13 | |

*p = 0.008

Abbreviations: CDDP, cisplatin; CTX, cyclophosphamide; MMC, mitomycin-C1; MTX, methotrexate; VDS, vindesine.
PC, prior chemotherapy; PI, prior irradiation; NT, no prior treatment; SQ, squamous cell carcinoma; AD, adenocarcinoma; LC, large cell carcinoma; CR, complete response; PR, partial response.

then every 6 weeks. Among the 375 patients assessible for response, only 58 (15%) achieved objective response. Single agent vindesine every 2 weeks resulted in a response rate of less than 1%, while the response rate on the other two arms was 27% and 19%, respectively. There was no statistically significant survival difference among the treatment arms with median survival being 15 months (vindesine), 20 weeks (vindesine plus mitomycin C), and 25 weeks (vindesine plus cisplatin), respectively. In a prognostic factor analysis, treatment was not a significant factor for survival.

Another study was reported by Einhorn *et al.* [30] with 124 evaluable patients randomized to vindesine versus vindesine plus cisplatin 120 mg/m$^2$ versus cisplatin 60 mg/m$^2$ plus vindesine plus mitomycin-C. The dose of vindesine was in this study 3 mg/m$^2$ weekly × 5 and thus higher than in the previous study by Luedke *et al.* [29]. The higher dose resulted also in a higher response rate, 14% (6 of 42 patients, confidence limits 5–29%) and the results support the observation in the study from Copenhagen indicating that the dosage of vindesine *per se* is an important factor for response.

Among the other studies, only the results from Elliot *et al.* [31] yielded a significant response and survival benefit for combination chemotherapy (vindesine plus cisplatin) as compared to vindesine alone with response rates of 27% versus 6% and survival of 46 versus 17 weeks based on a study including 54 and 51 patients in each arm.

Noteworthy are also the results from minor studies indicating a higher response rate of vindesine compared to a combination of doxorubicin and cyclophosphamide (25% versus 5%) in a study with 28 patients in each arm [33]. In another investigation, vindesine was compared to vincristine with 35 and 28 patients with non-small cell lung cancer

*Table 6.* Summary of vindesine as single agent in randomized trials

| Schedule mg/m² i.v. | No. of patients | | | | Response | | | | 95% Confidence limits | Duration of response (weeks) | Duration of survival | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PC | PI | NT | Total | CR | PR | Total | % | | | | |
| 4 weekly × 8, then q. 2 weeks | 0 | 0 | 71 | 71 | 5 | 11 | 16 | (22) | 13–34 | 12 | 29 | 28 |
| 3 q. 2 weeks | 0 | 45 | 83 | 128 | 0 | 1 | 1 | (1) | 0–11 | 12 | 15 | 29 |
| 3 weekly × 5, then q. 2 weeks | 0 | – | 42 | 42 | 0 | 6 | 6 | (14) | 5–29 | 14 | 18 | 30 |
| 3–4 weekly × 8, then 3 q. 2 weeks | 0 | | 54 | 54 | 0 | 3 | 3 | (6) | 1–15 | – | 17 | 31 |
| 3 q. 2 weeks | 0 | 4 | 13 | 17 | 0 | 3 | 3 | (18) | 5–53 | – | – | 32 |
| 3 weekly × 10, then q. 2 weeks | 0 | 0 | 28 | 28 | 0 | 7 | 7 | (25) | 11–44 | 7 | 14 | 33 |
| 3 weeks × 10, then q. 2 weeks | 0 | – | – | 35 | 0 | 5 | 5 | (14) | 5–30 | – | 16 | 34 |
| Overall results | | | | 375 | 5 | 36 | 41 | (11) | 8–15 | | | |

Abbreviations: see Table 5.

treated. The response rates were 14% and 0%, respectively, with no differences in survival data (16 weeks versus 13 weeks) [34].

In Table 6, the summary includes a total of 375 patients treated with vindesine at various dose levels in phase III trials, yielding a response rate of 11% (confidence limits 8–15). The latter is within the same range as observed from the phase II trials (Table 4). Table 6, however, includes 128 patients equalling one third of all patients treated at a suboptimal dose of vindesine given at 3 mg/m² every two weeks.

## Combination chemotherapy

### *Phase III trials*

The effect of vindesine as part of combination chemotherapy has been evaluated in several randomized studies, and it will be described under the following headings:

1. Comparison of combination chemotherapy regimens with substitution of vindesine by other drugs (Table 7).
2. Comparison of combination chemotherapy regimens with and without vindesine (Table 8).
3. Comparison of different vindesine containing chemotherapy regimens (Table 9).
4. Comparison of combination of vindesine plus cisplatin against supportive care only (Table 10).

### *Comparison of combination chemotherapy regimens with substitution of vindesine by other drugs (Table 7)*

Vindesine has been substituted by other drugs in 7 randomized studies (Table 7).

Gatzemeier *et al.* [35] reported on a three-arm study comparing vindesine plus mitomycin-C to combinations of either ifosfamide plus mitomycin-C or etoposide and cisplatin. None of 192 evaluable patients had received prior chemo- and radiotherapy and all had bidimensionally measurable indicator lesions. Vindesine was given as a 3 mg/m² i.v. injection on days 1 and 8 every 4 weeks. The dose of mitomycin-C was 10 mg/m² day 1 every 4 weeks in both treatment arms which included this compound. Thus, the study allows a randomized comparison of vindesine against ifosfamide given as 1.8 mg/m² day 1 to 5 infusion including uroprotection with mesna. No differences in antitumour activity were noted as overall response rate to the vindesine/mitomycin arm was 23% against 30% in the ifosfamide/mitomycin arm and against 25%

*Table 7.* Comparison of combination chemotherapy regimens with substitution of vindesine by other drugs

| Treatment | No. of patients | | | | Histology (%) | | | Response | | | | 95% Confidence limits (%) | Median duration of response (weeks) | survival | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PC | PI | NT | Total | SQ | AD | LC | CR | PR | Total | (%) | | | | |
| VDS/MMC | 0 | 0 | 66 | 66 | 46 | 36 | 18 | 0 | 15 | 15 | (23) | (13–35) | – | 23 | |
| IFX/MMC | 0 | 0 | 66 | 66 | 56 | 18 | 26 | 2 | 18 | 20 | (30) | (20–43) | – | 27 | 35 |
| VP16/CDDP | 0 | 0 | 60 | 60 | 55 | 20 | 25 | 3 | 12 | 15 | (25) | (15–38) | – | 25 | |
| VDS/CDDP | 0 | 19 | 29 | 48 | 29 | 61 | 10 | 2 | 14 | 16 | (33) | (20–48) | 34 | – | 36 |
| VBL/CDDP | 0 | 18 | 31 | 49 | 20 | 78 | 2 | 3 | 17 | 20 | (41) | (27–56) | 22 | – | |
| VDS/CDDP | 0 | 30 | 68 | 91 | 31 | 46 | 20 | 1 | 21 | 22 | (25) | (15–32) | – | 33** | |
| CTX/DX/CDDP | 0 | 27 | 73 | 92 | 25 | 51 | 17 | 0 | 13 | 13 | (15) | (7–21) | – | 25** | 6 |
| Supportive care | 0 | 17 | 36 | 53 | 24 | 48 | 24 | – | – | – | – | – | – | 17 | |
| VDS/CDDP | 0 | 8 | 23 | 31 | 52 | 32 | 16 | 3 | 12 | 15 | (48)*** | (30–67) | 22 | 43 | |
| VP-16/CDDP | 0 | 4 | 29 | 33 | 45 | 33 | 21 | 2 | 10 | 12 | (36)* | (20–55) | 17 | 47 | 37 |
| CTX/DX | 0 | 7 | 23 | 30 | 57 | 23 | 20 | 0 | 3 | 3 | (10)*** | (2–27) | 16 | 41 | |
| VDS/CDDP | 0 | 42 | 82 | 124 | 39 | 44 | 15 | 6 | 26 | 32 | (25) | (19–36) | 12 | 26 | |
| VP-16/CDDP | 0 | 45 | 81 | 126 | 40 | 42 | 15 | 2 | 23 | 26 | (30) | (14–28) | 19 | 27 | 3 |
| CTX/DX/MTX/PCZ | 0 | 47 | 68 | 115 | 37 | 42 | 18 | 1 | 19 | 20 | (17) | (11–25) | 14 | 25 | |
| MMC/VBL/CDDP | 0 | 49 | 72 | 121 | 39 | 43 | 16 | 6 | 31 | 37 | (31) | (23–40) | 11 | 22 | |
| VDS/CDDP | 0 | – | – | 52 | 18 | 60 | 23 | 4 | 18 | 22 | (35) | (24–49) | 43 | 29 | |
| VP-16/CDDP | 0 | – | – | 57 | 37 | 51 | 12 | 3 | 17 | 20 | (30) | (19–42) | 20 | 29 | 38 |
| VDS/CDDP/VP-16 | 0 | – | – | 55 | 26 | 67 | 8 | 1 | 12 | 13 | (22) | (12–33) | 27 | 28 | |
| VDS/CDDP | 0 | 9 | 43 | 52 | 35 | 33 | 29 | 0 | 5 | 5 | (10)* | (3–21) | – | 25 | |
| VP-16/CDDP | 0 | 14 | 35 | 49 | 43 | 45 | 16 | 0 | 3 | 3 | (6)* | (1–17) | – | 17 | 39 |
| VDS/CDDP/VP-16 | 0 | 11 | 40 | 51 | 24 | 47 | 29 | 1 | 11 | 12 | (24)* | (13–37) | – | 20 | |

*p < 0.05, **p ≤ 0.01, ***p < 0.005
Abbreviations: DX, doxorubicin; IFX, ifosfamide; PCZ, procarbazine; VBL, vinblastine; VP-16, etoposide.
For other abbreviations, see Table 5.

*Table 8.* Comparison of combination chemotherapy regimens with and without vindesine.

| Treatment | No. of patients | | | | Histology (%) | | | Response | | | | 95% Confidence limits (%) | Median duration of response (weeks) | survival | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PC | PI | NT | Total | SQ | AD | LC | CR | PR | Total | (%) | | | | |
| VDS | 0 | 0 | 71 | 71 | 0 | 100 | 0 | 5 | 11 | 16 | (22) | (13–34) | 12 | 24 | |
| CCNU/CTX/MTX | 0 | 0 | 74 | 74 | 0 | 100 | 0 | 2 | 15 | 17 | (23) | (14–34) | 16 | 29 | 28 |
| VDS/CCNU/CTX/MTX | 0 | 0 | 73 | 73 | 0 | 100 | 0 | 2 | 18 | 20 | (27) | (18–39) | 16 | 34 | |
| CDDP(80mg/m²) | 0 | 0 | 78 | 78 | 34 | 56 | 10 | 0 | 9 | 9 | (12)* | (5–21) | 20 | 39 | 41 |
| VDS/CDDP | 0 | 0 | 77 | 77 | 35 | 61 | 4 | 0 | 22 | 22 | (29)* | (19–40) | 20 | 45 | |
| VDS/CDDP | 0 | – | – | 52 | 18 | 60 | 23 | 4 | 18 | 22 | (35) | (24–49) | 43 | 29 | |
| VP-16/CDDP | 0 | – | – | 27 | 37 | 51 | 12 | 3 | 17 | 20 | (30) | (19–42) | 20 | 29 | 38 |
| VDS/CDDP/VP-16 | 0 | – | – | 55 | 26 | 67 | 8 | 1 | 12 | 13 | (22) | (12–33) | 27 | 28 | |
| VDS/CDDP | 0 | 9 | 43 | 52 | 35 | 33 | 29 | 0 | 5 | 5 | (10)* | (3–21) | – | 25 | |
| VP-16/CDDP | 0 | 14 | 35 | 49 | 43 | 45 | 16 | 0 | 3 | 3 | (6)* | (1–17) | – | 17 | 39 |
| VDS/CDDP/VP-16 | 0 | 11 | 40 | 51 | 24 | 47 | 29 | 1 | 11 | 12 | (24)* | (13–37) | – | 20 | |

*p < 0.05
Abbreviations, see previous tables.

*Table 9.* Comparison of different vindesine-containing chemotherapy regimens

| Treatment | No. of patients | | | | Histology (%) | | | Response | | | | 95% Confidence limits (%) | Median duration of | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PC | PI | NT | Total | SQ | AD | LC | CR | PR | Total | (%) | | Response (weeks) | Survival | |
| VDS/CDDP (35 mg/m$^2$ days 1,8,15) | – | – | – | 24 | – | – | – | – | – | 6 | (25) | (10–47) | – | 38 | 43 |
| VDS/CDDP (80 mg/m$^2$ day 1) | – | – | – | 27 | – | – | – | – | – | 6 | (22) | (9–42) | – | 34 | |
| VDS/CDDP (60 mg/m$^2$ days 1,29, then q 6wks) | 0 | – | – | 41 | 34 | 66 | 0 | 3 | 16 | 19 | (46) | (31–63) | 22* | – | 42 |
| VDS/CDDP (120 mg/m$^2$ days 1,29 then q 6 wks) | 0 | – | – | 40 | 25 | 75 | 0 | 5 | 11 | 16 | (40) | (25–57) | 48* | – | |
| VDS/CDDP (80 mg/m$^2$ day 1 q 3 wks) | 0 | 0 | 21 | 21 | 19 | 67 | 14 | 0 | 7 | 7 | (33) | (15–57) | 25 | 41 | 44 |
| VDS/CDDP (120 mg/m$^2$ day 1 q 4 wks) | 0 | 0 | 23 | 23 | 25 | 75 | 0 | 1 | 8 | 9 | (39) | (20–61) | 31 | 49 | |
| VDS/CDDP | 0 | 0 | 11 | 11 | – | – | – | 2 | 5 | 7 | (64) | (31–89) | 42 | 42 | 45 |
| VDS/CTX | 0 | 0 | 16 | 16 | – | – | – | 0 | 5 | 5 | (31) | (11–59) | 23 | 16 | |
| VDS/MMC | 0 | 0 | 58 | 58 | 29 | 31 | 38 | 0 | 13 | 13 | (22)** | (13–35) | 12 | 28** | |
| Lonidamine | 0 | 0 | 58 | 58 | 29 | 31 | 38 | 0 | 2 | 2 | (3)** | (0–12) | – | 21** | 46 |
| VDS/MMC/Lonidamine | 0 | 0 | 54 | 54 | 22 | 26 | 52 | 0 | 14 | 14 | (26)** | (15–40) | 16 | 32** | |
| VDS/CDDP | 0 | 0 | 28 | 28 | 18 | 64 | 14 | 0 | 12 | 12 | (43)*** | (24–63) | 12 | 45 | 47 |
| VDS/MMC | 0 | 0 | 30 | 30 | 17 | 70 | 13 | 0 | 3 | 3 | (10)*** | (2–27) | – | 45 | |
| VDS | 0 | 45 | 83 | 128 | 31 | 44 | 25 | – | 1 | 1 | (1) | (0–4) | 12 | 15 | |
| VDS/MMC | 0 | 37 | 85 | 122 | 35 | 46 | 19 | 1 | 32 | 33 | (27) | (26–36) | 12 | 20 | 29 |
| VDS/CDDP | 0 | 30 | 95 | 125 | 34 | 45 | 21 | 2 | 22 | 24 | (19) | (13–28) | 12 | 25 | |
| VDS/CDDP | 0 | 0 | 63 | 63 | 13 | 68 | 13 | 0 | 14 | 14 | (23) | (14–34) | 23 | 41 | 48 |
| VDS/CDDP/MMC | 0 | 0 | 61 | 61 | 18 | 72 | 8 | 0 | 21 | 21 | (35) | (24–48) | 37 | 47 | |
| VDS/CDDP | 0 | 0 | 63 | 63 | 48 | 48 | 4 | 0 | 21 | 21 | (33) | (22–46) | – | 50 | 49 |
| VDS/CDDP/MMC | 0 | 0 | 68 | 68 | 38 | 54 | 7 | 1 | 28 | 29 | (43)** | (31–55) | – | 42 | |
| VP-16/CDDP alternating with VDS/MMC | 0 | 0 | 68 | 68 | 44 | 43 | 13 | 1 | 12 | 13 | (19)** | (11–30) | – | 40 | |

*Table 9.* Comparison of different vindesine-containing chemotherapy regimens

| Treatment | No. of patients | | | | Histology (%) | | | Response | | | | 95% Confidence limits (%) | Median duration of | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PC | PI | NT | Total | SQ | AD | LC | CR | PR | Total | (%) | | Response (weeks) | Survival | |
| VDS | 0 | – | – | 42 | 40 | 45 | 15 | 0 | 6 | 6 | (14) | (5–29) | 14 | 18 | 30 |
| VDS/CDDP | 0 | – | – | 41 | 46 | 46 | 8 | 0 | 11 | 11 | (27) | (14–43) | 23 | 26 | |
| VDS/CDDP/MMC | 0 | – | – | 41 | 41 | 49 | 10 | 0 | 8 | 8 | (20) | (9–35) | 27 | 17 | |
| VDS/CDDP/IFX | 0 | – | – | 50 | 58 | 28 | 14 | 1 | 9 | 10 | (20) | (10–34) | – | 30 | 50 |
| VDS/CDDP/MMC | 0 | – | – | 53 | 51 | 30 | 9 | 3 | 11 | 14 | (26) | (15–40) | – | 32 | |
| VDS/CDDP | 0 | 5 | 20 | 25 | 44 | 32 | 24 | 0 | 4 | 4 | (16) | (5–36) | – | 16 | 51 |
| VDS/MTX | 0 | 0 | 23 | 23 | 43 | 43 | 13 | 0 | 3 | 3 | (13) | (3–34) | – | 16 | |
| VDS/CDDP/CTX/DX | 0 | – | – | 35 | 28 | 70 | 2 | 2 | 6 | 8 | (24) | (10–40) | 40 | 32 | 52 |
| VDS/CDDP/CTX | 0 | – | – | 33 | | | | 2 | 10 | 12 | (36) | (20–55) | | | |
| VDS/CDDP | 0 | – | – | 52 | 18 | 60 | 23 | 4 | 18 | 22 | (35) | (24–49) | 43 | 29 | 38 |
| VP-16/CDDP | 0 | – | – | 57 | 37 | 51 | 12 | 3 | 17 | 20 | (30) | (19–42) | 20 | 29 | |
| VDS/CDDP/VP-16 | 0 | – | – | 55 | 26 | 67 | 8 | 1 | 12 | 13 | (22) | (12–33) | 27 | 28 | |
| VDS/CDDP | 0 | 9 | 43 | 52 | 35 | 33 | 29 | 0 | 5 | 5 | (10)* | (3–21) | – | 25 | 39 |
| VP-16/CDDP | 0 | 14 | 35 | 49 | 43 | 45 | 16 | 0 | 3 | 3 | (6)* | (1–17) | – | 17 | |
| VDS/CDDP/VP-16 | 0 | 11 | 40 | 51 | 24 | 47 | 29 | 1 | 11 | 12 | (24)* | (13–37) | – | 20 | |

*$p \leq 0.05$, **$p < 0.01$, ***$p < 0.005$
Abbreviations, see previous tables.

*Table 10.* Comparison of combinations of vindesine plus cisplatin against supportive care only

| Treatment | No. of patients | | | | Histology (%) | | | Response | | | | 95% Confidence limits (%) | Median duration of | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PC | PI | NT | Total | SQ | AD | LC | CR | PR | Total | (%) | | Response (weeks) | Survival | |
| VDS/CDDP | 0 | 30 | 68 | 91 | 31 | 46 | 20 | 1 | 21 | 22 | (25) | (16–34) | – | 33* | |
| CTX/DX/CDDP | 0 | 27 | 73 | 92 | 25 | 51 | 17 | 0 | 13 | 13 | (15) | (8–23) | – | 25 | 6 |
| Supportive care | 0 | 17 | 36 | 53 | 24 | 48 | 24 | – | – | – | – | – | – | 17* | |
| VDS/CDDP | 0 | – | – | 97 | 37 | 39 | 24 | 6 | 21 | 27 | (28) | (19–38) | 40 | 27 | 54 |
| Supportive care | 0 | – | – | 91 | 35 | 38 | 27 | – | – | – | – | – | – | 17 | |
| VDS/CDDP | 0 | – | – | 24 | 63 | 29 | 8 | 1 | 9 | 10 | (42) | (22–63) | – | 28** | 7 |
| Supportive care | 0 | – | – | 22 | 32 | 45 | 23 | – | – | – | – | – | – | 10** | |

*p = 0.01, **p < 0.001
Abbreviations, see previous tables.

response rate in the VP-16/cisplatin arm. There were no complete responses with the vindesine/mitomycin combination, while 2 and 3 complete responses were noted for the other two combinations, respectively. Also survival was similar with median survival of 23, 27, and 25 weeks, respectively. Based on these data, vindesine and ifosfamide have the same order of activity in NSCLC when given together with mitomycin-C.

With regard to toxicity, the combination of vindesine/mitomycin-C was significantly less toxic than the other two treatment arms, as nausea and vomiting (WHO grade 3 + 4) occurred in only 6.1% of the patients versus 43.3% of those treated with ifosfamide/mitomycin-C and 36.7% of those treated with VP-16/cisplatin ($p = 0.0001$).

With respect to neurotoxicity, mild peripheral neurotoxicity (WHO grade 1 + 2) occurred in 14% of patients treated with vindesine plus mitomycin-C as compared to none in the other two treatment arms. No patients discontinued treatment because of neurotoxicity.

A study by Kris *et al.* [36] included 97 patients with stage III NSCLC who were randomly assigned to receive cisplatin (120 mg/m$^2$) with either vindesine (3 mg/m$^2$ weekly for 5 weeks, then every other week) or vinblastine (6 mg/m$^2$ weekly for 5 weeks, then every other week) (Table 7). None had previously received chemotherapy. Both patients with evaluable and measurable indicator lesions were included. Response rates (33% versus 41%), median response duration (34 versus 22 weeks), and median survival times of responding patients (83 versus 73 weeks) were similar. Thus, vindesine and vinblastine yielded similar results when compared in this randomized fashion in combination with cisplatin.

Some degree of peripheral neuropathy occurred in all patients. Mild neuropathy (decreased deep tendon reflexes or paresthesias) was noted in 93% of the patients in both treatment arms, although symptoms appeared more rapidly in patients receiving vindesine. Moderate symptoms of weakness, activity-limiting paresthesias or paralytic ileus were observed in equal number of patients (7%). These symptoms occurred earlier in the course (2–12 weeks) of vindesine-treated patients than of vinblastine-treated patients (> 12 weeks). Clinically significant leukopenia was more common in patients treated with vinblastine than in those treated with vindesine (WBC < 2100/mm$^3$ in 53% versus 27%; $p = 0.003$) and more frequent hospitalizations for fever occurred during a period of drug-induced leukopenia (19% versus 8%; $p = 0.05$). Two patients died with fever during the period of drug-induced leucopenia – one in each treatment arm.

In conclusion, the two regimens demonstrated comparable response and survival data, but clinically significant leucopenia was more common in the vinblastine-treated patients.

A Canadian multicenter study by Rapp *et al.* [6] compared best supportive care to two chemo-

therapy regimens, vindesine and cisplatin, and cyclophosphamide, doxorubicin and cisplatin. The patients had either measurable or evaluable disease and none had received prior chemotherapy. Randomization was performed in two parts: 150 patients were randomized in the three-arm scheme, while centers choosing not to participate in a study with a no-chemotherapy arm followed a two-arm scheme comparing the 2-drug combination to the 3-drug combination (101 additional patients). In the 2-drug combination, the doses were as follows: vindesine 3 mg/m$^2$ i.v. weekly $\times$ 4, then every other week, cisplatin 120 mg/m$^2$ i.v. day 1 and day 29, then every 6 weeks. Treatment in the 3-drug combination was cyclophosphamide 400 mg/m$^2$ i.v., doxorubicin 40 mg/m$^2$ i.v. and cisplatin 40 mg/m$^2$ i.v. day 1 in each cycle repeated every 4 weeks. The overall response rates were 25% for vindesine/cisplatin and 15% for cyclophosphamide, doxorubicin, and cisplatin ($p = 0.06$). The median survival in the two treatment arms was 33 weeks and 25 weeks, respectively ($p = 0.01$). The dose of cisplatin was substantially higher in the vindesine/cisplatin regimen than in the 3-drug combination. A direct comparison of vindesine as a single agent to a combination of cyclophosphamide plus doxorubicin can therefore not be judged from this study. The impact of chemotherapy relative to supportive care will be discussed later in relation to Table 10.

The toxicity in this study was considerable, with leucopenia of severe or greater degree according to ECOG toxicity criteria occurring in 38% (cyclophosphamide plus doxorubicin plus cisplatin) and 40% (vindesine plus cisplatin). Toxicity was more pronounced in the vindesine/cisplatin arm with respect to severe vomiting occurring in 23% of the patients as compared with 12% for the other treatment arm (not significant). Severe neurotoxicity was noted in 16% of the patients as compared to 0% for patients receiving cyclophosphamide, doxorubicin plus cisplatin ($p < 0.001$). Based on these data, the combination of vindesine/cisplatin is superior to a combination of cyclophosphamide, doxorubicin and cisplatin with respect to survival and is approaching significant superiority with respect to response rate, but at the expense of severe neurotoxicity in 16% of the patients and a tendency toward more patients experiencing severe vomiting in the vindesine/cisplatin arm. Part of the differences might be explained by the markedly different cisplatin dosages.

Etoposide (VP-16) is a frequently used agent in NSCLC, especially in combination with cisplatin, and this combination has been the subject of numerous studies.

Paccagnella *et al.* [37] reported on a randomized study comparing vindesine plus cisplatin to VP-16 plus cisplatin and to doxorubicin plus cyclophosphamide. The dose of vindesine was 3 mg/m$^2$ weekly $\times$ 6, then every second week, while the cisplatin dose was 100 mg/m$^2$ day 1 every 4 weeks, both when given in combination with vindesine and with VP-16. The dose of VP-16 was 125 mg/m$^2$ days 1, 3 and 5 every 4 weeks, while the doses of cyclophosphamide and doxorubicin were 700 mg/m$^2$ and 40 mg/m$^2$, respectively, every 3 weeks. All 94 patients had measurable disease. Forty-eight percent responded to vindesine plus cisplatin, 36% to VP-16 plus cisplatin and 10% to doxorubicin plus cyclophosphamide (vindesine plus cisplatin versus doxorubicin plus cyclophosphamide, $p < 0.005$; VP-16 plus cisplatin versus doxorubicin plus cyclophosphamide, $p < 0.05$; vindesine plus cisplatin versus VP-16 plus cisplatin, not significant). There were no significant differences in either duration of response or survival for the three groups (Table 7).

Hematologic and neurologic toxicities were significantly higher in the vindesine/cisplatin-containing regimen than in the two other combinations. A granulocyte count of less than 0.9 $\times$ 1000/mm$^3$ (severe and life-threatening toxicity) was recorded in 26%, 6% and 21% of the patients, respectively, making granulocytopenia statistically more frequent in the vindesine/cisplatin and the doxorubicin/cyclophosphamide arms than in the VP-16/cisplatin arm ($p < 0.05$). Renal toxicity was experienced by 4 patients (18%) receiving vindesine plus cisplatin and by 4 (10%) receiving VP-16 plus cisplatin. Peripheral neuropathy was observed in 57% of the patients receiving the vindesine/cisplatin regimen and in only 3% and 6% of patients receiving the VP-16/cisplatin regimen and the

doxorubicin/cyclophosphamide regimen ($p < 0.001$).

Based on these results, it may be concluded that the combination of vindesine plus cisplatin is significantly more active with respect to response rate than a combination of doxorubicin plus cyclophosphamide. The regimen of vindesine plus cisplatin has a marginally higher response rate than VP-16 plus cisplatin, which does not reach a significant level. The duration of response and survival are similar. The high activity with the vindesine plus cisplatin regimen is thus achieved at the expense of significantly higher toxicity with respect to granulocytopenia and peripheral neuropathy.

Also the Eastern Cooperative Oncology Group (ECOG) conducted a prospective, randomized trial including the regimen of vindesine plus cisplatin [3]. Four of the most active chemotherapy regimens for metastatic NSCLC were evaluated (Table 7), including a vindesine/cisplatin arm. The vindesine dose was 3 mg/m$^2$ weekly $\times$ 5 then every other week and the cisplatin dose was 120 mg/m$^2$ days 1, 29 and then every 6 weeks. Dose of VP-16 was 120 mg/m$^2$ days 4, 6, and 8 together with cisplatin 60 mg/m$^2$ day 1 with cycles repeated every 3 weeks. In the 4-drug regimen, the doses were cyclophosphamide 300 mg/m$^2$, doxorubicin 20 mg/m$^2$, and methotrexate 15 mg/m$^2$ – all 3 drugs given days 1 and 8, while procarbazine dose was 100 mg/m$^2$ days 2 through 11, repeated every 4 weeks. The dose of mitomycin-C was 10 mg/m$^2$ together with vinblastine 6 mg/m$^2$ and cisplatin 40 mg/m$^2$ – all 3 drugs given day 1 every 3 weeks.

A total of 468 patients with either measurable or evaluable disease was randomized in the study. The response rate to vindesine/cisplatin was 25%, while it was 30% for patients receiving VP-16 plus cisplatin and 17% and 31%, respectively, for the 4-drug and 3-drug regimens (not significant). Breaking up the results according to histology, the response rate for the mitomycin-C/vinblastine and cisplatin regimen was significantly higher compared to the other 3 regimens grouped together for patients with squamous and adenocarcinoma ($p = 0.02$). The vindesine plus cisplatin regimen had the highest response rate for large cell carcinoma (37%) as compared to 32%, 14%, and 16%, respectively, for the other regimens, but the result is not significant because of the small number of cases. The differences in response rate had no impact on survival, which was similar for all treatment regimens, and neither did duration of response differ by treatment. The 4-drug regimen was significantly less toxic than the other regimens ($p < 0.001$). The vindesine plus cisplatin regimen demonstrated significantly more life-threatening (7 patients) and lethal (3 patients) episodes of nephrotoxicities ($p < 0.001$) than the other treatment arms, despite an aggressive hydration program that in itself caused significant morbidity.

Based on these results, no regimen stands out as a clearly superior treatment. The high frequency of severe nephrotoxicity to the vindesine/cisplatin regimen can undoubtedly be attributed to the considerably higher cisplatin dose used in this particular regimen.

A comparison of vindesine to VP-16, both drugs in combination with cisplatin, has also been made by Dhingra *et al.* [38]. A total of 164 patients without prior chemotherapy were randomized to receive either vindesine plus cisplatin or VP-16 plus cisplatin, or vindesine plus VP-16 plus cisplatin. The dose of vindesine in combination with cisplatin was 3 mg/m$^2$ weekly $\times$ 7 and then every other week, while the dose of vindesine in combination with VP-16 plus cisplatin was 3–3.5 mg/m$^2$ once every 3 weeks. The dose of cisplatin varied from 120 mg/m$^2$ day 1, 28 and then every 6 weeks in combination with vindesine, to 60–80 and 50–80 mg/m$^2$ every 3 weeks in combination with either VP-16 or vindesine plus VP-16, respectively. Also the dose intensity of VP-16 varied from 120 mg/m$^2$ day 4, 6 and 8 every 3 weeks in combination with cisplatin to a dose of 50 to 80 mg/m$^2$ day 4, 6 and 8 every 3 weeks in combination with vindesine plus cisplatin. Highest response rate (35%) was obtained with the vindesine plus cisplatin treatment arm, though this was not statistically superior to the 30% response rate obtained with VP-16 plus cisplatin and the 22% obtained with vindesine plus VP-16 plus cisplatin. Response durations were 43, 20, and 27 weeks, respectively, while the median survival was 29, 29, and 28 weeks, respectively for the three treatment arms. The differences were statistically

insignificant. Myelosuppression was similar in all treatment arms, but significant more azotemea, defined as an increase of the serum creatinine level to 1.5 mg/cl and/or creatinine clearance < 60 ml/min occurred in the vindesine/cisplatin treatment arm (46% of the patients) ($p = 0.002$). A significantly high incidence of peripheral neuropathy, defined as subjective or objective evidence of sensory nerve impairment with or without deep tendon reflex diminution occurred in both treatment arms incorporating cisplatin and vindesine in the combination. The frequency of neuropathy in the vindesine/cisplatin arm was 33% which was significantly higher than compared to the other two treatment arms ($p = 0.003$) while lowest incidence of peripheral neuropathy occurred in the VP-16/cisplatin arm with 5% of patients affected ($p = 0.005$). The combination of vindesine plus VP-16 plus cisplatin was intermediate with 21% of patients affected by peripheral neuropathy. The only two patients having to discontinue chemotherapy due to severe neuropathy were treated in the vindesine/cisplatin arm. In conclusion, all the treatment arms had similar antitumour activity, though with non-significant tendency toward a higher response rate and longer response duration among patients receiving vindesine plus cisplatin, but with significantly more neurotoxicity and azotemea in the vindesine/cisplatin arm compared to the VP-16/cisplatin regimen. It is not possible in this study directly to compare the activity of vindesine and VP-16 as the dose intensity of cisplatin varied between the two drug treatment arms.

Hainsworth *et al.* [39] also evaluated the combination of vindesine plus cisplatin as compared to VP-16 plus cisplatin and to vindesine plus VP-16 plus cisplatin. None of the patients had received prior chemotherapy and they all had either measurable or evaluable lesions. One fifth of the patients had received prior irradiation therapy. The dose and schedule of the three treatment arms were somewhat different from that of Dhingra *et al.* [38] especially with respect to cisplatin. In the vindesine plus cisplatin arm, the vindesine dose was the same as in the above-mentioned study, while the cisplatin dosage was 60 mg/m$^2$ every 4 weeks as compared to 120 mg/m$^2$ in the study by Dhingra *et al.* With respect to the regimen with VP-16 plus cisplatin, the dose of VP-16 was 100 mg/m$^2$ day 1 and 7 every 4 weeks, while the cisplatin dose was the same as in the vindesine/cisplatin arm. Similar dosages and schedules were applied for all three drugs in the vindesine plus VP-16 plus cisplatin regimen. The study design thus enables a direct comparison between vindesine and VP-16 as the cisplatin dosage schedule is similar for the two treatment arms.

The results were disappointing, as the response rates for the three regimens were 10%, 6% and 24%, respectively. The 3-drug regimen produced more responses than did the 2-drug combinations ($p < 0.05$). However, median survival was not improved with the 3-drug regimen (Table 7), and the myelosuppression was more pronounced. Overall, the three regimens were not equitoxic as the number of patients with WBC < 1000/mm$^3$ were 11, 1, and 11 patients, respectively in the regimens of vindesine plus cisplatin, VP-16 plus cisplatin, and vindesine plus VP-16 plus cisplatin. The corresponding number of patients with infection related deaths was 1, 0 and 2. The number of patients with peripheral neuropathy were 9, 0, 11, respectively, while nephrotoxicity as defined as creatinine level > 2.0 mg/dl was not observed in any of the treatment regimens.

The lower response rate obtained with the regimen of vindesine and cisplatin and with the regimen of VP-16 plus cisplatin in the study by Hainsworth *et al.* [39] as compared to the study by Dhingra *et al.* [38] may be attributed to the lower dose intensity of cisplatin in this study, especially in the vindesine plus cisplatin arm. Also the categorizations of patients who did not complete the 6 week induction regimen as non responders tend to lower the apparent response rate. In some trials patients have not been included in the response evaluation unless they received at least two doses of cisplatin, e.g. in the study by Dhingra *et al.* [38]. In the current trial, the response rate of patients who remained on study at the 8 week re-evaluation point was 19%. As most of the early drop-outs were due to progressive disease, these patients were most appropriately classified as non-responders. In conclusion, vindesine and VP-16 in the applied doses and schedules revealed similar low activity, though the two regimens

were not equitoxic as the vindesine plus cisplatin combination resulted in more leucopenia and peripheral neuropathy. Comparing the three regimens it appears that none of these regimens were associated with high activity in NSCLC. Although the addition of vindesine to VP-16 plus cisplatin probably increases the response rate slightly, the overall impact of the addition of the drug was not significant. None of the studies revealed superiority of VP-16 and cisplatin containing regimens versus vindesine and cisplatin containing regimens.

*Comparison of combination chemotherapy regimens with and without vindesine (Table 8)*

Four studies have evaluated the effect of additional vindesine to another chemotherapy regimen in a randomized fashion (Table 8). In a study by Sørensen *et al.* [28] vindesine as a single agent was compared to a combination of CCNU/cyclophosphamide/methotrexate and also compared to a combination of all four drugs. The dosage of vindesine as single agent was 4 mg/m$^2$ weekly for 8 weeks, then every second week, while in the 3-drug combination regimen, the dose schedule for CCNU was 70 mg/m$^2$ orally and cyclophosphamide 1000 mg/m$^2$ i.v. every 4 weeks, and methotrexate 20 mg/m$^2$ orally day 15 and 18 of each course. The reason for selecting the latter combination was the results of previous studies showing that CCNU plus cyclophosphamide and methotrexate were superior to cyclophosphamide plus methotrexate in adenocarcinoma of the lung [40].

The same schedule applied in the 3-drug regimen was also used in the 4-drug regimen, but the dosage was lower for CCNU (50 mg/m$^2$), cyclophosphamide (700 mg/m$^2$) and vindesine (2 mg/m$^2$). A total of 259 patients were included and were evaluable for survival; response assessment was possible in 218 patients. All patients had adenocarcinoma of the lung. Response rates were similar in the three treatment arms (22%, 23%, and 27%, respectively) as were median durations of response (12 weeks, 16 weeks, and 16 weeks, respectively) and survival (24 weeks, 29 weeks and 34 weeks, respectively). Complete remission was achieved in 7% of the patients treated with vindesine as single agent and in 3% of the patients in each of the two combination chemotherapy arms. Based on these results, vindesine as single agent was as active as both the 3-drug and 4-drug combination chemotherapy arm. Addition of vindesine to the combination of CCNU, cyclophosphamide and methotrexate did not enhance activity. However, the dose intensity of both vindesine, CCNU and cyclophosphamide was lower in the 4-drug combination chemotherapy regimen, which hampers firm conclusions on the effect of addition of vindesine to 3-drug combination chemotherapy arm.

In spite of the difference in dose intensity, no differences were observed in proportions of patients who received treatment without dose reduction with the vindesine regimen (15%), 3-drug (22%), or 4-drug treatment (17%). Neurotoxicity was the most common reason for dose reduction during vindesine treatment, with paresthesias necessitating dose reduction in 54% as compared to 0% and 24%, respectively for 3- or 4-drug regimens. Dose reduction was most commonly due to leucocytopenia in 3-drug (64%) and 4-drug treatment (59%). Based on these toxicity data, it does not seem feasible to increase dose intensity in the 4-drug regimen arm and thus the activity of the combination of CCNU, cyclophosphamide and methotrexate by addition of vindesine.

Cisplatin is a widely used agent in NSCLC and is part of several of the most active combination chemotherapy regimens. The activity of cisplatin as single agent (80 mg/m$^2$ on day 1) was compared to that of vindesine plus cisplatin (vindesine 3 mg/m$^2$ on day 1, 8 and 15) in a randomized study by Kawahara *et al.* [41]. None of the patients had previously received chemotherapy or radiotherapy and all had measurable disease and an ECOC performance status of 0–3. The treatment cycle was repeated every 4 weeks. Eighty patients were included in each arm, 78 patients were evaluable for response in the cisplatin arm, while 77 patients were evaluable in the combination chemotherapy arm. There were no complete remissions in either arm. The difference in overall response rate between the two arms (12% versus 29%) was statistically significant ($p < 0.05$). Median duration of response was 20 weeks for both

treatment arms. No statistically significant differences in the duration of response and survival were observed.

The incidence of myelosuppression (grade 3 or 4) was significantly greater in the combination arm than in the cisplatin-alone arm (40 versus 0 patients according to leucocyte count, $p<0.01$; 8 versus 1 patients according to platelet count, $p<0.05$). Grade 2 or 3 non-hematological toxicity such as nausea and vomiting, constipation, elevation of serum creatinin level, and partial hearing loss were evenly distributed in the two arms. However, grade 2 or 3 peripheral neuropathy (11 versus 2 patients, $p<0.05$) and alopecia (44 versus 1 patient, $p<0.01$) occurred much more frequently in the combination arm than in the cisplatin-alone arm. The toxicity was mild to moderate, reversible and manageable.

The dosage of cisplatin used in this study is moderate compared to what has been used in other studies. Although Gralla *et al.* [42] reported that a high dose cisplatin regimen (120 mg/m$^2$) in combination with vindesine was superior to a low dose cisplatin regimen (60 mg/m$^2$) in combination with vindesine both in median duration of response and median survival of responders, there were no differences in response rate and overall survival (Table 9). Thus, the conclusion from the present study is that a significantly higher response rate can be obtained by addition of vindesine to cisplatin (80 mg/m$^2$), although there was no survival benefit for patients receiving such treatment. The higher response rate with combination chemotherapy regimen is achieved at the expense of a significantly more pronounced toxicity. The lack of a survival advantage may be attributed to the fact that no complete responses were achieved.

A randomized trial of 3 combinations of cisplatin with vindesine and/or VP-16 was reported by Dhingra *et al.* [38]. The study is referred in Table 7 and showed that the treatment arms had similar antitumour activity. The combination of VP-16 plus cisplatin was slightly less toxic than the combination of vindesine plus cisplatin or vindesine plus VP-16 plus cisplatin. Thus, the addition of vindesine to a combination of VP-16 plus cisplatin did not enhance activity, and the activity of the combination of vindesine plus cisplatin is equal to that of VP-16 plus cisplatin with the dosage and schedule applied in this study.

The study by Hainsworth *et al.* [39] has also been described above in relation to Table 7. This study compared the addition of vindesine plus cisplatin to a combination of VP-16 plus cisplatin and to a combination of all 3 drugs together. It is concluded from the study that the combination of vindesine plus cisplatin and the combination of VP-16 and cisplatin in the applied dosage and schedule revealed similar activity, though with more patients experiencing toxicity with respect to leucopenia and peripheral neuropathy in the vindesine plus cisplatin arm. Although the combination of vindesine plus VP-16 plus cisplatin increased the response rate slightly, the overall impact of this treatment combination was not significant.

It may be concluded from the studies cited in table 8 that it has been documented that the combination of vindesine plus cisplatin is more active than cisplatin alone with respect to response rate, but not with respect to response duration or survival, and at the expense of more pronounced toxicity. Combinations of vindesine plus cisplatin have been equally active to combinations of VP-16 plus cisplatin, but at the expense of more neurotoxicity in 16% and a tendency towards more patients experiencing severe vomiting in the vindesine/cisplatin arm.

*Comparison of different vindesine-containing regimens (Table 9)*

A randomized comparison between different chemotherapy regimens with vindesine as part of the combination in two or more of the treatment arms has been performed in 15 studies (Table 9). Three studies have evaluated the effect of vindesine with cisplatin in different doses. In the study by Nagao *et al.* [43] the dose of vindesine was 3 mg/m$^2$ days 1, 8 and 15 in each of two treatment arms, while the dose of cisplatin was either 35 mg/m$^2$ days 1, 8 and 15 or 80 mg/m$^2$ day 1. Among the 61 patients included, the number of complete cases treated by the former administration schedule was 24 and by the latter schedule 27. The response rates

were 25% and 22%, respectively. The median survival times were 8.5 months and 7.5 months, respectively. Nausea and vomiting were significantly milder in the treatment with cisplatin 35 mg/m$^2$.

Gralla *et al.* [42] reported on a comparison of two dosage schedule of cisplatin in combination with vindesine. The vindesine dose of 3 mg/m$^2$ weekly for 6 weeks, then every other week, while the dosage of cisplatin was either 60 mg/m$^2$ (41 patients) or 120 mg/m$^2$ (40 patients), in both cases given days 1 and 29, then every 6 weeks. All patients had measurable disease and had not previously received chemotherapy. Overall response rate was 46% and 40%, respectively, but the high-dose cisplatin regimen was superior to the low-dose regimen in median duration of response, which was 12 versus 5.5 months ($p = 0.05$) and the median survival for responding patients which was 21.7 versus 10 months ($p = 0.02$). No difference was reported in overall survival between the two treatment arms.

The degree of myelosuppression experienced during the trial was similar for patients on the high-dose and low-dose cisplatin treatment. Nephrotoxicity, defined as a peak serum creatinine level above 1.4 mg/dl occurred in 38 patients. Three patients, all treated with high-dose cisplatin, had a rise in serum creatinine above 3.4 mg/dl, which in all cases returned to normal range without specific treatment. A progressive fall in creatinine clearance with a median decrease of 25% was observed among those patients who received 4 or more courses of cisplatin. Due to this decrease in renal function, 7 of the 16 responding patients on the high-dose regimen required attenuation of the cisplatin dose, as opposed to 5 of 19 responding patients on the low-dose arm ($p = 0.31$).

All patients experienced some degree of neurotoxicity which was correlated to the total dose of vindesine received. Neurotoxicity was similar in patients treated with either high or low doses of cisplatin. Thus, the two treatment arms with different doses of cisplatin were equally toxic and yielded similar response rates, but with a longer median duration of response and survival for responding patients among the patients receiving the high-dose cisplatin treatment.

Also, Shinkai *et al.* [44] evaluated two different doses of cisplatin in combination with vindesine. The vindesine dose was also in this study 3 mg/m$^2$, but was given weekly for 5 weeks and then every other week. The cisplatin dose was either 120 mg/m$^2$ every 4 weeks or 80 mg/m$^2$ every 3 weeks. All patients were previously untreated and had measurable disease. There were no differences observed in either response rate or median duration of response or survival (Table 9). Thrombocytopenia was more pronounced with high-dose cisplatin (median nadir of 119 $\times$ 10$^3$/mm$^3$) than with low-dose cisplatin (median nadir of 146 $\times$ 10$^3$/mm$^3$) ($p < 0.05$). Nephrotoxicity, defined as a peak serum creatinine value above 1.5 mg/dl occurred in 74% and 48% of patients treated with high-dose and low-dose cisplatin, respectively ($p < 0.05$). Peripheral neurotoxicity was noted in 35% and 38% of the patients, respectively.

It is concluded that high-dose cisplatin did not result in a significantly better response rate or a survival advantage, but was associated with more thrombocytopenia and nephrotoxicity.

Based on these three comparative studies evaluating the cisplatin dose in combination with vindesine, it may be concluded that high-dose cisplatin in the dose of 120 mg/m$^2$ days 1, 29 and then every 6 weeks yield longer median duration of response and median duration of survival for responders than cisplatin in a dosage of 60 mg/m$^2$ days 1, 29 and then every 6 weeks in combination with vindesine, as described by Gralla *et al.* [42]. However, cisplatin 120 mg/m$^2$ day 1 every 4 weeks is not associated with a higher activity than cisplatin 80 mg/m$^2$ every 3 weeks in combination with vindesine based on the results published by Shinkai *et al.* [44].

One study has evaluated the activity of vindesine plus cisplatin against that of vindesine plus cyclophosphamide [45] (Table 9). Eleven patients were treated with vindesine 3 mg/m$^2$ and cisplatin 120 mg/m$^2$; the schedule was not reported, and 16 patients received vindesine 3 mg/m$^2$ and cyclophosphamide 1 g/m$^2$. All patients had measurable tumours and had not been pretreated with chemotherapy. The response rate was 64% to the vindesine/cisplatin arm with 2 complete responses among the 11 patients treated compared to 31% in patients treated with vindesine/cyclophosphamide

without any complete responses (not significant). The median duration of response for the first combination was 42 weeks versus 23 weeks for the second combination. Median duration of survival was 42 and 16 weeks, respectively (not significant). In spite of the differences in response rate, median duration of response and survival, there were no statistically significant differences in the study owing to the low statistical power of the low number of patients included in each treatment arm.

Mitomycin-C is by many reported to be among the active cytostatic drugs in the treatment of non-small cell lung cancer and it has therefore been included in numerous studies. In Table 9, 7 studies describe the activity of vindesine plus mitomycin-C with or without the addition of other agents in comparison to treatments including vindesine plus cisplatin.

Gatzemeier *et al.* [46] evaluated the combination of vindesine 3 mg/m$^2$ days 1 and 8 and mitomycin-C 10 mg/m$^2$ day 1 every 4 weeks and compared it to treatment with lonidamine and to a treatment including all 3 drugs. The cytotoxic mechanism of lonidamine is different from that of commonly used anti-cancer agents, exerting an activity on cell energy metabolism by inhibition of glycolysis and cellular oxygen consumption. All patients had bidimensionally measurable disease and none had received previous chemotherapy or radiotherapy. In the lonidamine monotherapy arm, only two partial responses were seen (3%). Vindesine and mitomycin-C yielded 17 partial responses (22%) compared to 26% with the 3-drug combination. The response rate in the lonidamine-alone arm was statistically significantly lower than in the other two arms ($p < 0.01$). The median duration of response was 12 and 16 weeks, respectively for vindesine/mitomycin-C and the 3-drug combination. The median survival times were 21 weeks for lonidamine, 28 weeks for vindesine/mitomycin-C and 32 weeks for the 3-drug combination, resulting in a statistically significant survival difference between the two chemotherapy groups and lonidamine alone ($p < 0.01$). The toxicity observed with mitomycin-C and vindesine was only mild, without major differences between regimens. It is concluded that combination chemotherapy with vindesine plus mitomycin-C plus or minus lonidamine has a significantly higher response rate than treatment with lonidamine alone and can prolong survival significantly without severe toxicity.

Shinkai *et al.* [47] compared the activity of vindesine plus mitomycin-C to vindesine plus cisplatin. Vindesine 3 mg/m$^2$ was given in both treatment regimens weekly for the first 5 weeks, then every other week. The dose of mitomycin-C was 8 mg/m$^2$ weekly for 3 weeks, then every 3 weeks, while the cisplatin dose was 80 mg/m$^2$ days 1, 22 and 43 and then every 6 weeks thereafter. All patients were previously untreated. Among the 28 patients treated with vindesine plus cisplatin, there were 12 partial responders (43%) as compared to 3 partial responders (10%) among the 30 patients treated with vindesine plus mitomycin-C. Median survival times for patients in both treatment arms were 45 weeks.

Thrombocytopenia ($< 75 \times 10^3$/mm$^3$) occurred more frequently in patients treated with vindesine plus mitomycin-C (50%) than in the vindesine plus cisplatin arm (14%). Peak serum creatinine levels $> 1.5$ mg/dl were found in 13 (47%) of the 28 patients treated with vindesine plus cisplatin in contrast to only 1 patient in the vindesine plus mitomycin-C treatment regimen. No patients developed severe renal insufficience. The frequency of patients with peripheral neurotoxicity was 32% and 50%, respectively. These toxic effects were generally manageable. The combination of vindesine and cisplatin appears to be more effective than the combination of vindesine plus mitomycin-C with respect to response rate, but not survival.

This aspect was further evaluated by Luedke *et al.* [29], who randomized 375 patients to either vindesine alone or a combination of vindesine plus mitomycin-C or a combination of vindesine plus cisplatin. The dose of vindesine as single agent was 3 mg/m$^2$ every 2 weeks, while the dose was 3 mg/m$^2$ weekly for 5 weeks in the two combination chemotherapy arms. The mitomycin-C dose was 20 mg/m$^2$ day 1 and then 15 mg/m$^2$ every 6 weeks, while the cisplatin dose was 120 mg/m$^2$ days 1, 29 and then every 6 weeks. None of the patients had received prior chemotherapy, but some had received prior irradiation (Table 9). The dose inten-

sity in the single agent vindesine treatment arm was less than half of the dose intensity used in other randomized studies with vindesine as single agent and, correspondingly, only one partial remission was observed among 128 patients treated. The response rate for the two combination chemotherapy arms were 27% and 19%, respectively (not significant). Median duration of response was 12 weeks in all three treatment arms, while median survival times were 15 weeks, 20 weeks and 25 weeks, respectively. The survival curve of patients receiving vindesine plus cisplatin achieved borderline significance compared with patients treated with vindesine alone ($p < 0.06$), but in the prognostic factor analysis, treatment was not a significant factor for survival ($p = 0.47$).

Vindesine alone produced few significant side effects and when mitomycin-C was added to vindesine, little serious toxicity was added except for neutropenia ($p < 0.01$). Thus, the principal finding of the study was that the two combination chemotherapy regimens revealed equal activity and did not give a significant survival advantage over minimal therapy.

Both vindesine, mitomycin-C and cisplatin have been widely used in various combinations in the treatment of patients with advanced NSCLC. The potential therapeutic benefit of the addition of mitomycin-C to vindesine plus cisplatin has been evaluated in three randomized trials and the results of these are reported by Shinkai *et al.* [48], Fukuoka *et al.*, [49] and Einhorn *et al.* [30] (Table 9).

In the study by Shinkai *et al.* [48], 63 patients received vindesine plus cisplatin, while 61 patients received vindesine/cisplatin plus mitomycin-C. In the 2-drug combination, the dosage of vindesine was 3 mg/m$^2$ weekly for 5 weeks then every second weeks and of cisplatin 80 mg/m$^2$ days 1, 22 and 42, then every 6 weeks. In the three-drug regimen, mitomycin-C 8 mg/m$^2$ was given on day 1, while vindesine 3 mg/m$^2$ was given on days 1 and 8, and cisplatin 80 mg/m$^2$ on day 1, then every 4 weeks for 3 courses then every 6 weeks. No patients in the study achieved a complete response. Partial response rates in the 2-drug and 3-drug combinations were 23% versus 35% ($p = 0.13$), respectively. The median duration of response was 23 versus 37 weeks ($p = 0.071$), respectively, while median survival times were 41 and 47 weeks. No differences in the frequency of side effects were observed, except that WHO grade 3 and 4 leucopenia was higher in the 3-drug regimens. Thus, the addition of mitomycin-C to the regimen of vindesine plus cisplatin appears to have only limited value, if any.

The objective of the study by Fukuoka *et al.* [49] was also to compare vindesine plus cisplatin to vindesine, cisplatin and mitomycin-C and in addition a treatment arm with VP-16 plus cisplatin alternating with vindesine plus mitomycin-C was included. Among 199 assessible patients, the response rate to the 2-drug regimen was 33% compared to 43% for the 3-drug regimen, and 19% with the alternating regimen. The addition of mitomycin-C to the vindesine/cisplatin regimen did not significantly improve the response rate, and the response rate was significantly lower with the alternating regimen than with the vindesine/cisplatin/mitomycin-C regimen ($p < 0.01$). The median survival times were 50 weeks, 42 weeks, and 40 weeks for the 2-, 3- and 4-drug treatment, respectively ($p > 0.05$). Grade 3 or 4 thrombocytopenia was significantly greater ($p < 0.01$) in patients receiving vindesine/cisplatin/mitomycin-C (22%) than in patients receiving vindesine/cisplatin (5%). Other types of toxicity were similar. It may be concluded from these two studies that the addition of mitomycin-C to the combination of vindesine plus cisplatin yields a tendency towards a higher activity with respect to response rate and in one of the studies also with respect to response duration, but not at a statistically significant level and at the expense of more pronounced toxicity.

In contrast, Einhorn *et al.* [30] did not observe a trend towards higher activity when mitomycin-C was combined with vindesine plus cisplatin (Table 9). In this study, patients with both measurable as well as with evaluable were included. The study was a 3-arm study comparing vindesine 3 mg/m$^2$ weekly $\times$ 5, then every other week with vindesine in the same dose and schedule in combination with high-dose cisplatin 120 mg/m$^2$ days 1 and 39 then every 6 weeks and also compared to a 3-drug regimen with vindesine in the same dose and schedule, cisplatin 60 mg/m$^2$ days 1 and 29 then every 6

weeks and mitomycin-C 12 mg/m$^2$ days 1 and 29, then every 6 weeks. The objective response rates were 14%, 27%, and 20%, respectively, and the median survival times were 18, 26, and 17 weeks, respectively. The study failed to demonstrate sufficient therapeutic benefit for vindesine and cisplatin compared to single agent vindesine. In contrast to the studies by Shinkai *et al.* [48] and Fukuoka *et al.* [49] no trend was observed toward a higher activity with inclusion of mitomycin-C. The frequency of severe hematologic toxicity was 23% of patients treated with both the 2-drug and the 3-drug combination chemotherapy and significantly more nephrotoxicity (serum creatinine > 2 ml) occurred in each of these two combination chemotherapy regimens. There were 4 drug-related deaths in the entire patient population, all occurring in the 3-drug regimen. Thus, the study failed to demonstrate sufficient therapeutic benefit for vindesine, cisplatin and mitomycin-C to justify the increased morbidity as reflected in the occurrence of treatment-related deaths.

In an attempt to increase the activity of the combination of vindesine plus cisplatin, Rosell *et al.* [50] added ifosfamide or mitomycin-C to the vindesine/cisplatin combination in a two-arm randomized study. Doses of vindesine were similar in the two treatment arms while the cisplatin dose was 120 ml/m$^2$ on days 1 and 29, then every 6 weeks in the mitomycin-C containing regimen, whereas in the ifosfamide-containing regimen, the cisplatin dose was 100 mg/m$^2$. Among the patients evaluable for response, the response rate was 26% in the mitomycin-C containing regimen compared to 20% in the ifosfamide-containing regimen. Neither response rate nor the median survival times were significantly different. WHO grade 1 nephrotoxicity was observed in 43% of the patients in the mitomycin-C-containing regimen versus 26% in the ifosfamide-containing regimen ($p = 0.04$). Both treatment arms were disappointing, and they could not support the use of a third drug to the combination of vindesine plus cisplatin, because of a possible deleterious effect with significant toxicity.

Another vindesine-containing combination was reported by Harvey *et al.* [51] who compared combination of vindesine plus cisplatin to a combination of vindesine plus methotrexate in an attempt to reduce the potential neurotoxicity of the former combination and also to assess the role of cisplatin. The dose and schedule of vindesine were similar in both studies with the vindesine dose being 3 mg/m$^2$ weekly for 7 weeks then every second week. The dose of cisplatin was 60 mg/m$^2$, while the methotrexate dose was 200 mg/m$^2$; both drugs were given day 1 and then every fourth week. No complete remissions were observed and the response rate was only 16% to the vindesine/cisplatin combination versus 13% to the vindesine plus methotrexate combination. Median survival was 16 weeks in both treatment arms. Nausea and vomiting were most prominent side effects in the vindesine/cisplatin arm (75% against 36%) while, surprisingly, mild neuropathy WHO grade 1 occurred more in the vindesine/methotrexate arm (40% against 18%, respectively). Renal dysfunction was uncommon, but occurred to a mild degree (WHO grade 1) in 18% of patients receiving vindesine plus cisplatin.

The response rates of 13% and 16% in the arms of the study were disappointing and also the survival was short. Contributing to this low response rate may be both patients factors such as the inclusion of both patients with measurable as well as evaluable disease and treatment factors, as the cisplatin dose was somewhat lower than used in most studies. However, the regimen of vindesine plus cisplatin was used in the same dose and schedule as reported by Gralla *et al.* [34] who observed a response rate of 46%, emphasizing the difference in distribution of various known and unknown prognostic factors that may differ between studies.

Early studies by Eagan *et al.* [4] and by Gralla *et al.* [19] reported a noteworthy activity of the 3-drug combination of cyclophosphamide, doxorubicin and cisplatin. A study by Kelsen *et al.* [52] was designed to assess the effects of the addition of doxorubicin and/or cyclophosphamide on the activity obtained with vindesine plus cisplatin. Seventy-eight patients were randomized to receive either vindesine, cisplatin, cyclophosphamide and doxorubicin or vindesine, cisplatin and cyclophosphamide. The cisplatin dose was 120 mg/m$^2$ every 6 weeks and of vindesine 3 mg/m$^2$ days 1 and 15 in

each 3 week cycle in both treatment arms. The dosage of doxorubicin dose was 13 mg/m$^2$ day 1 in each 3 week cycle, while the cyclophosphamide dose was 200 mg/m$^2$ in the 4-drug regimen and 500 mg/m$^2$ in the 3-drug regimen day 1 in each 3-week cycle. Response rates for the two treatment arms were similar, being 24% for the 4-drug treatment and 36% for the 3-drug treatment, respectively (Table 9). Thus, the addition of doxorubicin to the 3-drug regimen did not yield superior results. There was no control arm including solely vindesine and cisplatin and thus the effect of inclusion of either cyclophosphamide or cyclophosphamide plus doxorubicin to the 2-drug regimen cannot be established from this study.

Two studies [38,39] both evaluated vindesine plus cisplatin as compared to VP-16 plus cisplatin to a combination of all 3 drugs. Both studies have been described in detail in relation to table B and give somewhat different results. It may be concluded from these two studies that the combination of vindesine plus cisplatin and the combination of VP-16 plus cisplatin reveal similar activity, although the two regimens are not equitoxic as the vindesine plus cisplatin combination revealed more patients with leucopenia and peripheral neuropathy. Although the 3-drug combination of vindesine/cisplatin/VP-16 results in a significantly higher response rate as compared to the regimen of vindesine plus cisplatin and VP-16 plus cisplatin in the study by Hainsworth *et al.* [39], this was not the case in the study by Dhingra *et al.* [38]. The overall impact of the 3-drug regimen is not significant as survival is similar among the 3 treatment regimens.

Based on the randomized studies in Table 9, some conclusions on the role of vindesine-containing chemotherapy regimens in the treatment of NSCLC can be drawn. Firstly, the optimal dose of cisplatin has not been established. Three different studies focused on this problem and evaluated different doses and schedules of cisplatin against each other, which, however, have not resulted in statistically significant differences in response rate or overall survival. One study by Gralla *et al.* [42] observed an advantage with high-dose cisplatin (120 mg/m$^2$) in contrast to low-dose cisplatin (60 mg/m$^2$) with respect to median duration of response and with respect to survival of responding patients, pointing towards a slight advantage for the high-dose cisplatin at the expense of more pronounced toxicity. The combination of vindesine plus cisplatin has also been evaluated against several other combinations and has been significantly superior with respect to response rate when compared against vindesine plus mitomycin-C (Shinkai *et al.* [44]), though other studies focusing on this issue have failed to demonstrate similar differences.

Addition of mitomycin-C to the combination of vindesine plus cisplatin has in two out of three studies shown a non-significant tendency towards a higher response rate and in one of the studies also a non-significant tendency towards longer duration of response. The combination of vindesine plus cisplatin is equally active as the combination of VP-16 plus cisplatin in two studies both with respect to response rate and survival, while a 3-drug combination of vindesine/cisplatin/VP-16 in one study has shown significantly higher response rates than each of the two 2-drug regimens, but still with activity on a very modest level. Of interest is also the publication of superior survival for patients receiving vindesine plus mitomycin-C as compared to patients receiving treatment with lonidamine, although the difference of about 2 months on overall survival is not impressive. On the other hand, this trial demonstrates a survival advantage for NSCLC patients receiving chemotherapy as compared to minimal therapy and the trial suggests that a survival advantage is possible without regimens including cisplatin.

*Comparison of combinations of vindesine plus cisplatin against supportive care only (Table 10).*

The role of chemotherapy in advanced NSCLC has for years been a matter of dispute in medical oncology and has been the subject of a recent review [53]. What chemotherapy can offer is known from many reports, but to assess the impact of chemotherapy on survival in relation to what can be achieved by supportive care only needs control studies and in recent years several of such studies have been published. In 5 of these studies, vindesine has been part

of the chemotherapy, in all cases in combination with cisplatin as shown in the 5 studies in Table 10. The Canadian multicenter study by Rapp *et al.* [6] includes accumulated results from two trials. Trial A is a 3-arm study comparing best supportive care (53 patients) to patients receiving cyclophosphamide, doxorubicin and cisplatin (48 cases) and to patients receiving vindesine and cisplatin (49 cases); trial B is a 2-arm study comparing cyclophosphamide, doxorubicin and cisplatin (49 patients) to vindesine and cisplatin (47 patients) without the best-supportive-care arm. The pooled data are shown in Table 10. In the vindesine/cisplatin arm the vindesine dose was 3 mg/m$^2$ weekly $\times$ 4, then every 2 weeks, while the cisplatin dose was 120 mg/m$^2$ days 1, 39 and then every 6 weeks. The patients had measurable or evaluable disease and had not received prior chemotherapy but some patients had received prior irradiation (Table 10). The overall response rates on the chemotherapy arms were 25% for vindesine and cisplatin and 15% for cyclophosphamide, doxorubicin, and cisplatin ($p = 0.06$). Patients had a median survival of 33 weeks when receiving vindesine and cisplatin, 25 weeks when receiving cyclophosphamide, doxorubicin and cisplatin, and 17 weeks with best supportive care. The results indicate significantly prolonged survival with vindesine and cisplatin when compared to best supportive care ($p = 0.01$). The comparison of cyclophosphamide, doxorubicin and cisplatin versus best supportive care approached significance. Thus, the trial showed that the administration of chemotherapy consisting of vindesine and cisplatin can improve in a modest way the overall survival of treated patients with advanced NSCLC.

Woods *et al.* [54] updated an earlier report by Williams *et al.* [55] on an Anglo-Australian study comparing a regimen of vindesine plus cisplatin to best supportive care. Vindesine dose was 3 mg/m$^2$ weekly for 6–7 weeks then every second week, while cisplatin was given as 120 mg/m$^2$ every 4 weeks. Median survival was 27 weeks for patients in the chemotherapy arm and 17 weeks in the best-supportive-care arm (not significant). Analysis of the patients with limited disease showed a median survival of 43 weeks for the chemotherapy arm and 26 weeks for the non-treatment arm ($p = 0.13$) [47]. Toxicity was severe in the treatment arm, as all patients experienced subjective toxicity, 18% had WHO grade 3–4 myelotoxicity and 23% had grade 3–4 nausea and vomiting. The study fails to show a statistically significant survival advantage with chemotherapy, but there is a modest trend towards improved overall survival in patients with limited disease treated with chemotherapy, though at the expense of toxicity.

A recent study by Quoix *et al.* [7] also evaluates the combination of vindesine plus cisplatin against supportive care. The dose of vindesine was 3 mg/m$^2$ weekly $\times$ 5 then every second week and the cisplatin dose was 120 mg/m$^2$ every 4 weeks. The study was rather small, with only 24 patients in the chemotherapy group and 22 in the best supportive care group. Toxicity in the chemotherapy arm grade 3 or more was observed in 18% with respect to neutropenia with 1 death related to treatment. Overall response rate in the chemotherapy group was 42%. The patients in the chemotherapy group had a median survival of 28 weeks, while patients receiving solely best supportive care had a median survival time of 10 weeks ($p < 0.001$). None of the patients receiving chemotherapy had neuropathy WHO grade 3 or worse, while 18% had neutropenia WHO grade 3 or worse.

Based on the studies cited in Table 10, two of the three studies comparing vindesine plus cisplatin to best supportive care showed a significant but modest survival advantage for patients receiving chemotherapy. Also, in the last study by Woods *et al.* [54] the longest median survival was observed in the chemotherapy arm, though not significant.

## Neoadjuvant chemotherapy including vindesine (Table 11)

Between 30–40% of patients with NSCLC have advanced disease confined to the chest (stage III disease) at the time of diagnosis. In the new international staging classification, stage III NSCLC has been divided into stage IIIa and stage IIIb. Although there is a small difference in survival between these two subgroups, the overall prognosis

for stage III disease is poor because only 10% of patients are cured [56]. Surgery offers the only realistic chance of long-term survival, but even in patients with complete resection 5-year survival is only 30% [57].

The dismal results of treatment of stage IIIa NSCLC with surgery has led to investigation of combination chemotherapy. Chemotherapy has in several studies been used in an adjuvant setting after operation in an attempt to increase survival. In addition to the use in a postoperative setting, chemotherapy has also been evaluated before surgery (neoadjuvant chemotherapy) in stage IIIa lung cancer. Despite its evaluation in more than 500 patients, no firm conclusions can currently be made about its value [56]. This is partly due to problems in study design, such as the use of single arm studies with short durations of follow-up. Comparison between studies is hampered by marked heterogeniety of the patient population studied, lack of consensus about the role of staging mediastinoscopy, and disagreement over the precise definition of the resectable stage III disease [58]. In addition, most patients enrolled in these studies have been highly selected.

One study has evaluated the role of neoadjuvant chemotherapy with vindesine in NSCLC. Bitran *et al.* [59] included 23 patients with stage IIIa or stage IIIb disease and employed an initial chemotherapy regimen of vindesine (3 mg/m$^2$ weekly $\times$ 6); cisplatin (120 mg/m$^2$ days 1 and 22); VP-16 (300 mg/m$^2$ weekly $\times$ 6), followed by surgery and postoperative radiotherapy (54 Gy, 17 fractions). Eligibility requirements were histologically confirmed NSCLC with T3 lesions and histologically confirmed superior mediastinal or ipsilateral superclavicular nodal involvement. Of the 23 patients included, 3 patients were excluded because of early death before day 21 (2 patients) or an erroneous diagnosis (1 patient). All of the remaining 20 patients had mediastinoscopy to document mediastinal involvement. After completion of 6 weeks of chemotherapy with vindesine/cisplatin/VP-16, all patients were restaged.

No complete remissions were achieved, while partial remissions occurred in 14 patients, resulting in a response rate of 70% among the 20 patients surviving through day 21 and a response rate of 61% among all patients included in the study. A total of 7 patients had no medical contraindications to undergo surgery, but 4 refused and 3 underwent thoracotomy. In 2 of the 3 patients, who underwent lobectomy, only microscopic tumour was found within the lung. The remaining patients had visible, but resectable microscopic tumour adherent to the chest wall. After resection, postoperative radiotherapy was administered, 54 Gy in 17 fractions to a part that included the ipsilateral hilum, mediastinum and both superclavicular fossa. All patients who had a medical contraindication to surgery, or refused surgery, also received the same irradiation. The median survival for the 20 patients who survived until day 21 was 39 weeks. The actuarial 1 year survival rate was 34%.

Toxicities to the chemotherapy included nausea and vomiting and moderate to total alopecia in all patients, numbness (13/20 patients) and cisplatin induced ototoxicity (4/20 patients); no patient developed renal insufficiency. Median nadir of leucocyte count on day 15 was 2.5 $\times$ 10$^3$/mm$^3$. There were two treatment related deaths, one due to septicemia, one due to inability to eat or drink after radiotherapy.

The study was updated by Vokes *et al.* [60] and the results are shown in Table 11. A total of 27 patients were included , 23 patients were evaluable, 13 had a partial response and 4 patients underwent resection. The median survival for all 27 patients in the study was 36 weeks.

Also Martini *et al.* [61] evaluated neoadjuvant chemotherapy with inclusion of vinka alkaloids. The chemotherapy regimens used included either vindesine plus cisplatin (8 patients), vindesine, cisplatin and mitomycin-C (8 patients), or vinblastine, cisplatin and mitomycin-C (42 patients). Overall data for these three regimens together are reported, but the effect of the vindesine-containing regimens cannot be extracted.

The response rate to the regimen of vindesine/cisplatin/VP-16 is described in the study by Bitran *et al.* [59] and by Vokes *et al.* [60] and is similar to the response rate reported in other neoadjuvant trials including regimens such as vinblastine, VP-16 and mitomycin-C [62], VP-16/cisplatin and 5-fluorouracil [63], cisplatin, bleomycin and

*Table 11.* Neoadjuvant chemotherapy including vindesine

| Treatment | Patients | | Stages included | Histology | | | Response rate (%) | Resection rate (%) | Rate of pathological CR (%) | Median survival (weeks) | 5-year survival (%) | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (n) | (n eval.) | | SQ | AD | LC | | | | | | |
| VDS/CDDP/VP-16 | 27 | 23 | IIIa,IIIb | 33 | 44 | 22 | 48–56* | 13–15* | 0 | 36 | NR | 59 |

* Lowest rate = rate for all pts included; highest rate = rate for evaluable patients; NR = Not reported
Abbreviations, see previous tables.

mitomycin-C [64] and in two studies using mitomycin-C, a vinca alkaloid and cisplatin [60,61]. However, survival varied widely among these studies dependent on the patient population included. No randomized study on this topic has been published and thus it is not possible to extract the precise role of vindesine in a neoadjuvant setting.

## Adjuvant chemotherapy including vindesine

A limited number of controlled clinical trials of adjuvant chemotherapy in NSCLC have been performed in both Europe and the US in recent years and these data have been summarized by Marangolo and Fiorentini [65]. Most of these studies have failed to demonstrate a survival advantage from postoperative chemotherapy. However, adjuvant chemotherapy as administered in a recent Lung Cancer Study Group (LCSG) trial produced a significantly longer disease-free survival and a 7-month increase in overall survival compared with adjuvant immunotherapy in stage II and IIIa, non-squamous cell lung cancer [66]. Although the study has been criticised because of its lack of an untreated control arm, it does suggest that the addition of chemotherapy to surgery may improve survival for some patients with locally advanced NSCLC.

One study has used vindesine as part of an adjuvant treatment [67]. A total of 68 patients had been resected in NSCLC stage I–III (intraoperative staging) and were stratified according to lymph node status and randomized to either adjuvant irradiation or a combination of adjuvant irradiation plus chemotherapy (vindesine 2 mg/m$^2$ and cisplatin 60 mg/m$^2$ in 6 cycles). A one-year disease-free survival of 49% was observed with adjuvant radiotherapy and 61% of patients receiving the combined treatment had a one-year disease-free survival (not significant). The overall survival was not reported.

Adjuvant chemotherapy in NSCLC is still at an experimental level and the exact role of vindesine in this setting has not been established.

## Combined radiotherapy with chemotherapy (Tables 12 and 13)

Patterns of failure analysis in NSCLC demonstrate that both local regional occurrence and distant metastases are major problems. This applies to those patients receiving definite resection as well as patients with inoperable disease receiving radiotherapy. Accordingly, several studies have investigated the role of combined modality treatments to improve these results on both local control and distant metastases. The results from 4 studies including vindesine in the chemotherapy regimens in combination with radiotherapy are listed in Table 12. The range of differences in patterns of failure following radiotherapy or inoperable disease is considerable and the outlook with respect to survival varies according to known and unknown prognostic factors in the patient population, making it difficult to draw firm conclusions on the use of combined modality treatment. To overcome this obstacle, several randomized studies have evaluated the effect of combined treatment in NSCLC and four studies using vindesine in the chemotherapy arm are shown in Table 13.

A study by Johnson *et al.* [72] compared the sur-

*Table 12.* Combined modality treatment including vindesine, phase II trials

| Chemotherapy | Radiotherapy | No. of patients | Histology (%) SQ | AD | LC | Stage | Response to chemotherapy (%) | Total response no. CR | PR | Total (%) | Median duration Response (weeks) | Survival | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VDS/CDDP/ CCNU/CTX | 60 Gy, 24 fractions | 33 | *100* | *0* | *0* | IIIa, IIIb | (42) | 18 | 6 | 24 (73) | – | 72 | 68 |
| VDS/CDDP/ IFX/DX | 48 Gy 16 fractions | 36 | 61 | 17 | 6 | I,IIIa IIIb, IV | (33) | 3 | 9 | 12 (33)* | – | 38 | 69 |
| VDS/CDDP/ VP-16 | 50 Gy, 25 fractions | 38 | – | – | – | – | (45) | 10 | 13 | 23 (61) | – | 65 | 70 |
| VDS/CDDP | 58 Gy | 22 | 64 | 27 | 9 | IIIa, IIIb | – | – | – | – – | – | 68 | 71 |

* Response data for chemotherapy only.
Abbreviations, see previous tables.

vival of patients with locally advanced NSCLC treated with single agent vindesine, thoracic radiotherapy, or both treatment modalities. The study included 319 patients with locally advanced unresectable NSCLC without evidence of extrathoracic metastases. All patients had measurable disease. Patients were randomly assigned to receive vindesine 3 mg/m$^2$ weekly for 6 weeks, then every other week or receive thoracic radiotherapy 60 Gy over 6 weeks or both vindesine and thoracic radiotherapy. Response assessment took place at week 6.

Overall response rate was superior in the radiotherapy arm (radiotherapy alone, 25%; radiotherapy plus vindesine, 28%; vindesine alone, 9%; $p = 0.001$). However, no improvement in survival was seen in the radiotherapy arms (Table 13). It is concluded from the study that patients with inoperable, non-metastatic NSCLC gain no survival advantage with thoracic irradiation as compared to treatment with vindesine alone.

In a Finnish trial, Niitamo-Korhonen *et al.* [73] randomized 72 previously untreated patients with localized inoperable NSCLC to either vindesine plus cisplatin or VP-16 plus cisplatin, both combined with split-course radiotherapy. Vindesine dose was 4 mg/m$^2$ weekly for 4 weeks, then every 2 weeks for 16 weeks and subsequently only in conjunction with cisplatin. Cisplatin was administered in a dose of 120 mg/m$^2$ days 1, 28 and 70, and again, beginning 28 days after the completion of radiotherapy, every 6 weeks to a total treatment time of 1 year. VP-16 was given on days 1–5 at a dosage of 60 mg/m$^2$ always in conjunction with cisplatin. Because of severe adverse effects in the first nine patients, the doses were reduced to vindesine 3 mg/m$^2$, cisplatin 90 mg/m$^2$ and VP-16 50 mg/m$^2$. Radiotherapy, beginning 4 weeks after the start of third chemotherapy cycle, was administered as 55 Gy in 22 fractions over 7–9 weeks.

The response rate to chemotherapy only was 51% for vindesine plus cisplatin and 43% for VP-16 plus cisplatin. All response rates are calculated according to the intention-to-treat principles. Radiotherapy increased the response rate to 65% and 57%, respectively. There were no differences in either duration of response or duration of survival (Table 13).

Based on these results, the antitumour effect of vindesine plus cisplatin and that of VP-16 plus cisplatin is similar. However, these chemotherapy regimens used in combination with radiotherapy resulted in a survival similar to but not better than what has previously been reported with either modality given alone.

In a randomized trial started in 1981, Van Houtte *et al.* [74] randomized 59 patients to either chest irradiation alone or 3 induction cycles of vindesine/cisplatin and VP-16 followed by chest irradiation. The dose of vindesine was 1.5 mg/m$^2$ days 1 and 8, etoposide 120 mg/m$^2$ days 2, 4 and 8 and cisplatin 60 mg/m$^2$ day 1 with cycles repeated every 4 weeks. Radiation was 55 Gy in 5.5 weeks. Of 27

patients treated with induction chemotherapy, 5 achieved a complete or partial remission after chemotherapy alone (19%). Following irradiation, the total response rate was 30% in the combined modality as compared to 53% in the radiotherapy alone arm. Survival was similar in the two treatment arms (Table 13). It is concluded that a chemotherapy program including vindesine, cisplatin and etoposide in the current dosage and schedule given before a course of thoracic irradiation in NSCLC did not improve the response rate nor the survival.

In a French multicentre trial, Le Chevalier *et al.* [75] randomized 353 patients with NSCLC stage IIIa or stage IIIb to receive either 3 cycles of induction chemotherapy with vindesine, cisplatin, CCNU, and cyclophosphamide followed by radiation and then 3 additional cycles of chemotherapy compared with radiation therapy alone. Doses in the chemotherapy regimen were: vindesine, 1.5 mg/m$^2$ days 1 and 2; cisplatin, 100 mg/m$^2$ day 2; CCNU, 50 mg/m$^2$ day 2 and 35 mg/m$^2$ day 3; and cyclophosphamide, 200 mg/m$^2$ days 2 through 4. Treatment was repeated every 4 weeks. The radiation therapy schedule was 5 fractions per week to a total dose of 65 Gy in 6.5 weeks. Induction chemotherapy produced a 26% objective response rate before initiaion of radiation according to intention-to-treat principles. There is a statistically significant difference in the rate of appearance of distant metastases favouring the combined modality arm ($p = 0.001$). However, local control at 1 year was poor in both groups despite the 65 Gy radiation treatment plan. In their first publication, there was no statistically significant difference in overall survival ($p = 0.08$). The median survival was 45 weeks for radiation alone versus 54 weeks for sequential chemotherapy and radiation. In a subsequent correspondence, a significant difference was observed in favour of the combined treatment. Three years' survival was 14% versus 21% and 4% versus 12%, respectively [76].

Based on these four randomized studies it may be concluded that the response rate to vindesine as a single agent is significantly lower than the response rate for either radiotherapy alone or the combined treatment of vindesine plus radiotherapy, as documented in the study by Johnson *et al.* [72]. Chemotherapy including vindesine, cisplatin, CCNU and cyclophosphamide in combination with radiotherapy exerted a significantly lower presence of distant metastases when compared to radiotherapy alone, but the effect on metastases did not have a significant impact on overall survival. Nor did the differences in response rate observed by Johnson *et al.* [72] influence the survival of the patients.

**Overall conclusions on vindesine activity in non-small cell lung cancer**

As a single agent, vindesine yields a response rate of 18% based on the treatment of 295 patients included into phase II trials (95% confidence limits (13–22). No difference is observed among the 3 major histologic types of NSCLC. In phase III trials, the response rate and confidence limits are at a similar level.

The activity of vindesine as compared to that of other drugs, based on an indirect comparison of combination chemotherapy regimens with substitution of vindesine by other drugs is listed in Table 7. Gatzemeier *et al.* [35] showed that vindesine was as active as ifosfamide, both given in combination with mitomycin-C, with respect to response rate and survival. Also the combination of vindesine plus mitomycin-C was significantly less toxic than ifosfamide plus mitomycin-C.

An indirect comparison of vindesine to vinblastine, both in combination with cisplatin, was made by Kris *et al.* [36] showing equal activity of vindesine and vinblastine in this setting. There was a non-significant tendency towards higher response rate in the vinblastine combination and towards longer duration of response in the vindesine combination. There were significantly more patients with leucopenia with vinblastine treatment compared to the vindesine-containing regimen.

The regimen of vindesine plus cisplatin was significantly superior with respect to survival as compared to the regimen of cyclophosphamide, doxorubicin and cisplatin in the study by Rapp *et al.* [6], and approached significant superiority with respect to response rate ($p = 0.06$). The dose of

cisplatin was, however, substantially higher in the vindesine/cisplatin regimen and thus a direct comparison of vindesine as single agent to a combination of cyclophosphamide/doxorubicin cannot be evaluated. The higher activity for the 2-drug combination was achieved at the expense of more pronounced toxicity, especially with respect to neurotoxicity.

Four studies have shown that the activity of a regimen of vindesine plus cisplatin is as active as that of VP-16 plus cisplatin, both with respect to response rate and with respect to survival [3,37–39]. However, the regimen of vindesine plus cisplatin revealed significantly higher toxicity with respect to granulocytopenia or peripheral neuropathy in several of these studies [37–39].

Four studies have evaluated the effect of single agent or combination chemotherapy with or without inclusion of vindesine (Table 8). From one of these studies it may be concluded that the combination of vindesine plus cisplatin is significantly more active than cisplatin alone with respect to response rate, but not with respect to duration of response and survival and at the expense of more pronounced toxicity [41]. The response rate of the vindesine/cisplatin combination has been significantly enhanced by the addition of VP-16 in one study [39], but not in another [38].

Comparison of different chemotherapy regimens containing vindesine has been outlined in Table 9. The relative activity of vindesine plus cisplatin and VP-16 plus cisplatin has been mentioned above. Most studies have used vindesine in combination with cisplatin, but it should be noted that the optimal dose of cisplatin has not been established, although one study [42] has observed an advantage with high-dose cisplatin (120 mg/m$^2$) in contrast to low-dose cisplatin (60 mg/m$^2$) with respect to median duration of response and survival of responding patients, but not with respect to response rate and overall survival.

The combination of vindesine plus cisplatin has been significantly superior with respect to response rate when compared with vindesine plus mitomycin-C [64]. Three studies have shown that vindesine/cisplatin is equally active as the combination of vindesine/cisplatin plus mitomycin-C [30,48, 49].

It has not been documented that the addition of one or two other drugs to the combination of vindesine plus cisplatin yields an increase in survival [3,38,39,51,52].

*Vindesine with or without other drugs versus best supportive care*

Three studies outlined in Table 10 have compared combinations of vindesine plus cisplatin against supportive care only. Two of the three studies showed a significant but modest survival advantage for patients receiving chemotherapy [6,7]. Also in the study by Woods *et al.* [53] was the longest median survival observed in the chemotherapy arm, although it was not significant.

Gatezemeier *et al.* [46], comparing minimal therapy consisting of lonidamine against a combination of either vindesine plus mitomycin-C or a combination of all three drugs. The authors observed a significantly increased response rate and significantly increased survival for the two latter regimens as compared to lonidamine alone. The difference of about 2 months on overall survival is not impressive, but the study is interesting as it demonstrates a survival advantage for NSCLC patients receiving chemotherapy as compared with patients receiving only minimal therapy, suggesting that a survival advantage is possible without regimens including cisplatin.

The observation of prolonged survival with chemotherapy regimens including vindesine leads to the conclusion that there is a role for vindesine in the treatment of NSCLC. However, the concept of chemotherapy in this disease remains investigational even though the advances seen in recent years clearly merit further studies.

*Vindesine-containing chemotherapy before or after surgery*

The results of trials with neoadjuvant chemotherapy including vindesine are shown in Table 11 and also the results of adjuvant chemotherapy including vindesine have been mentioned above. The data

*Table 13.* Combined treatment including vindesine, randomized phase III trials

| Chemotherapy | Radiotherapy | No. of patients | Histology (%) SQ | AD | LC | Stage | Response to chemotherapy (%) | Total response rate no. CR | PR | Total | (%) | Median duration of Response (weeks) | Survival | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VDS | None | 106 | – | – | – | I,II,IIIa, IIIb | (9) | 0 | 10 | 10 | (9)* | 16 | 45 | |
| vs | | | | | | | | | | | | | | |
| None | 60 Gy, 35 fractions | 106 | – | – | – | | – | 4 | 22 | 26 | (25)* | 17 | 39 | 72 |
| vs | | | | | | | | | | | | | | |
| VDS | 60 Gy, 35 fractions | 107 | – | – | – | | – | 2 | 28 | 30 | (28)* | 22 | 42 | |
| VDS/CDDP | 55 Gy, 22 fractions | 37 | 78 | 11 | 11 | I,II,III | (51) | 5 | 19 | 24 | (65) | 40 | 55 | 73 |
| vs | | | | | | | | | | | | | | |
| VP-16/CDDP | 55 Gy, 22 fractions | 35 | 71 | 6 | 23 | | (43) | 5 | 15 | 20 | (57) | 34 | 58 | |
| VDS/CDDP/ VP-16 | 55 Gy, 27 fractions | 27 | 70 | 15 | 15 | IIIa, IIIb | (19) | – | – | 8 | (30) | – | 50 | 74 |
| vs | | | | | | | | | | | | | | |
| None | 55 Gy, 27 fractions | 32 | 59 | 28 | 13 | | – | – | – | 17 | (53) | – | 50 | |
| VDS/CDDP/ CCNU/CTX | 65 Gy, 26 fractions | 176 | 85 | 0 | 15 | IIIa,IIIb | (26) | 26 | 25 | 51 | (29) | – | 54 | 75 |
| vs | | | | | | | | | | | | | | |
| None | 65 Gy, 26 fractions | 177 | 86 | 0 | 14 | | – | 33 | 26 | 59 | (33) | – | 45 | |

*$p < 0.01$
Abbreviations, see previous tables.

available do not allow conclusions on the precise role of vindesine in these settings.

*Combined modality treatment including radiotherapy in combination with chemotherapy containing vindesine*

Data on this issue are outlined in Table 12 and 13. Based on the four randomized studies in Table 13, it may be concluded that the response rate to vindesine as a single agent is significantly lower than that of either radiotherapy alone or for the combined treatment of vindesine plus radiotherapy. However, the duration of response and survival was similar. Noteworthy is the recent publication by Le Chevalier *et al.* [75] demonstrating a significant survival advantage for the combined use of radiotherapy plus chemotherapy (4 drugs including vindesine) versus radiotherapy alone, with 3-year survival being 12% versus 4% in a randomized trial with 353 patients with locally advanced NSCLC.

The equal activity of combinations of vindesine plus cisplatin as compared with combination of VP-16 plus cisplatin discussed above is also sustained through the effect of these two regimens in combination with irradiation, both with respect to response rate and duration of response and survival [72].

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